Clinical Evaluation of an Adaptive Decision Support System for Insulin Dose Adjustment in Type 1 Diabetes

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Abstract

The calculations required for insulin bolus dose adjustment in type 1 diabetes (T1D) may be complex. An automated standard bolus calculator has been shown to reduce dosing errors and decrease HbA1c although this may be at the expense of hypoglycaemia. It is not able to automatically adjust settings in response to changes in insulin sensitivity. The Advanced Bolus Calculator for Type 1 Diabetes (ACB4D) is an adaptive decision support system (DSS) comprising a real-time bolus calculator displayed on a smartphone application, used with real-time continuous glucose monitoring and a web-based clinician's platform. The ABC4D app runs in adaptive bolus calculator (intervention) or non-adaptive bolus calculator (control) mode.

This thesis outlines the clinical evaluation of the ABC4D in adults with T1D using multiple daily injections. Its safety and efficacy has been evaluated in an 8 month prospective randomised controlled non-inferiority crossover study. Participants underwent a 2 week run-in period, were randomised to intervention or control for 12 weeks, followed by a 6 week washout period and were crossed over to the other arm for the last 12 weeks.

There were no differences in glycaemic outcomes between ABC4D and control. The increase in diabetes treatment satisfaction score from baseline was lower with ABC4D compared to control. Participants accepted a lower percentage of all and meal doses during the last 2 weeks of ABC4D compared to control, with a greater reduction in meal doses from that recommended.

Whilst the ABC4D was safe, it did not demonstrate a glycaemic benefit compared to control. However ABC4D adaptations were performed automatically on participants' smartphones without requiring approval by a healthcare professional, which could save time in routine clinic appointments to then focus on other areas of diabetes care. Further research is needed to explore the barriers in the uptake of and trust in DSSs.

Declaration of Originality

The majority of the work in this thesis is my own and I have referenced all information from third parties accordingly. Collaboration and assistance has been detailed below:

Chapter 1:

The referenced systematic review was undertaken with Dr Pari Avari as co-reviewer. Dr Avari's contribution has been outlined in section 1.5.6.

Chapter 2:

The ABC4D system was developed by the engineering team at the Department of Electrical and Electronic Engineering, Imperial College London- Dr Pau Herrero, Mr Ryan Armiger and Mr Bernard Hernandez. The ABC4D web portal software was built by Bernard Hernandez. The ABC4D algorithm and system were developed by Mr Ryan Armiger and Dr Pau Herrero, who provided technical support throughout the study.

Ms Narvada Jugnee (research nurse) assisted with screening participants, blood sampling and urine testing, undertaking electrocardiograms (ECGs) and height, weight and blood pressure measurements and obtaining consent. Ms Narvada Jugnee took over the day-to-day running of the study when I started maternity leave. She conducted the outstanding study visits and telephone reviews (4^{th} study visits (n=2), 1 month telephone reviews (n=8) and 5^{th} study visits (n=15)), organised postal HbA1c samples, sent out study questionnaires, undertook data entry and downloaded data.

Ms Maria Thomas (project officer) assisted with the administration required for recruitment and study visits, with data entry and sending out supplies and study questionnaires to participants.

Chapter 3:

Mr Ryan Armiger provided assistance with the data cleaning, extraction and analysis. His contribution is detailed in section 3.9.

Copyright Declaration

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Abbreviations

ABC4D	Advanced Bolus Calculator for Type 1 Diabetes
AI	Artificial intelligence
AP	Artificial pancreas
ATTD	Advanced Technologies and Treatments for Diabetes
AUC	Area under the curve
BG	Blood glucose
CBR	Case-based reasoning
CDSS	Clinical Decision Support System
CGM	Continuous glucose monitoring
CHO	Carbohydrate
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
CV	Co-efficient of variation
DAFNE	Dose Adjusted for Normal Eating
DCCT	Diabetes Control and Complication Trial
DiAS	Diabetes Assistant
DIAS	Diabetes Advisory System
DKA	Diabetic ketoacidosis

DPV	Diabetes Prospective follow up registry
DQOL	Diabetes Quality of Life
DSS	Decision support system
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTTP	Diabetes Teaching and Treatment Programme
DVLA	Driver and Vehicle and Licensing Agency
ECG	Electrocardiogram
ED-DSS	Endo.Digital Decision support system
GAD	Glutamic acid decarboxylase
GI	Glycaemic Index
GMI	Glucose management indicator
HAATT	Hypoglycaemia Awareness, Anticipation and Treatment Training
HbA1c	Glycated haemoglobin
HCL	Hybrid closed loop
HCP	Health care provider
HFHP	High fat high protein
HLA	Human leucocyte antigens
IAA	Insulin autoantibodies
IA2	Tyrosine phosphatase islet antigen
ICA	Islet cell antibodies

ICER	Incremental cost effectiveness ratio
ICR	Insulin to carbohydrate ratio
IFCC	International Federation of Clinical Chemistry
IQR	Interquartile range
IS	Insulin sensitivity
isCGM	Intermittently scanned continuous glucose monitoring
ISF	Insulin sensitivity factor
ITT	Intention-to-treat analysis
JDRF	Juvenile Diabetes Research Foundation
KADIS	Karlsberg Diabetes Management System
LA	Learning algorithm
LBGI	Low blood glucose index
LFLP	Low fat low protein
MAG	Mean absolute glucose change per unit time
MAGE	Mean amplitude of glycaemic excursions
MARD	Mean absolute relative difference
MDI	Multiple daily injections
MPB	Model-Predictive bolus
MPC	Model-Predictive controller
NGSP	National Glycohaemoglobin Standardisation Programme

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAID	Problem Areas in Diabetes
PEPPER	Patient Empowerment through Predictive Personalised Decision Support
PID	Proportionate-integral-derivative
PIS	Participant information sheet
PLGS	Predictive low glucose suspend
QALY	Quality Adjusted Life Years
R2R	Run-to-run
ROC	Rate of change
RT-CGM	Real-time continuous glucose monitoring
SAE	Severe adverse event
SAP	Sensor augmented pump
Sars-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard deviation
SES	Socio-economic status
SG	Sensor glucose
SI	International system (units)
SMBG	Self-monitoring of blood glucose
T1D	Type 1 diabetes

T1DX	Type 1 Diabetes Exchange
TAR	Time above range
TBR	Time below range
TIR	Time in range
WHO	World Health Organisation
YSI	Yellow Springs Instrument
ZnT8	Zinc transporter-8

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Chapter 1: Introduction

1.1 Type 1 Diabetes

1.1.1 Epidemiology

The prevalence of diabetes worldwide in 20-79 year old adults was estimated to be 10.5% (536.6 million people) in 2021 and is predicted to rise to 12.2% (783.2 million people) in 2045 (1). There is geographical variation, with an estimated prevalence in 2021 of 12.2% in urban areas (360.0 million people) and 8.3% in rural areas (176.6 million) (1). It was estimated that there were 8.4 million individuals of all ages (95% uncertainty interval 8.1-8.8 million) worldwide with type 1 diabetes (T1D) in 2021 (2), which is predicted to increase to 13.5-17.4 million in 2040 (2). The National Diabetes Audit 2020-2021 in England and Wales showed there were 223,600 adults aged 19 years and over with T1D (3). This is an estimate of the prevalence, given that although 99.3% of General Practices participated in this audit, there were lower rates of engagement from specialist services (3), potentially impacting on the diagnosis validation process. The National Paediatric Diabetes Audit demonstrated that there were 29,892 children and young people (aged 0-24 years old) receiving care from a Paediatric Diabetes Unit (PDU) in 2020/2021 in England and Wales (4). 100% of PDUs submitted data for all patients receiving care from their services during this audit year (4). Whilst these adult and paediatric datasets may overlap in the case of young people aged 19-24 years old still under a PDU, they still serve to highlight the magnitude of the issue.

1.1.2 Pathogenesis

T1D is caused by autoimmune destruction of beta cells in the islets of Langerhans in the pancreas, leading to usually complete insulin deficiency. The traditional pathogenesis model

involves exposure to an environmental trigger activating an immune response in a genetically susceptible individual, leading to autoimmune beta cell destruction. Various triggers have been investigated but with unclear association, including viruses (such as coxsackie virus, rubella and recently Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2)), nutrients (such as early introduction of cow's milk) and toxins (5-7). A proposed newer complex model involves immune dysregulation secondary to interactions between susceptibility and protective genes (mainly in the human leucocyte antigens (HLA) genotypes DR and DQ) in combination with variable islet inflammation, influenced by environmental factors over a long period of time which act to stimulate or weaken disease during different stages of development (6, 8). For example, multiple infections during the first few years of life is associated with a reduction in the risk of developing T1D and loss of this effect with increasing sanitation, may in part explain why the frequency of T1D has increased (6).

A T-cell mediated immune response leads to inflammation in the islets of Langerhans (insulitis), in addition to B cells producing antibodies against beta cell antigens (8). The presence and persistence of multiple islet autoantibodies increases the risk of progression to overt diabetes, for example autoantibodies to islet cells (ICA), glutamic acid decarboxylase (GAD), protein tyrosine phosphatase islet antigen (IA2), insulin (IAA) (9) and zinc transporter-8 (ZnT8) (10) . This autoimmune destruction develops over several months or years, during which time individuals are euglycemic but have positive autoantibodies, until a large proportion of their beta cells are destroyed and consequently insulin levels reach a critically low level and symptoms become apparent (5). The prevalence of most autoantibodies are associated with age of diagnosis; IAA is highest is children <5 years old and decreases with age >10 years ($p < 0.001$), ZnT8 is higher in children > 5years old ($p=0.011$) and GAD increases with age >10 years ($p= 0.00016$) (11).

1.1.3 Clinical Features

Symptoms of new onset T1D include the classic triad of such as polyuria, polydipsia and weight loss. These symptoms develop due to the physiology of insulin deficiency and resulting hyperglycaemia. Hyperglycaemia leads to glycosuria and consequently an osmotic diuresis (12). This osmotic diuresis leads to the clinical feature of polyuria, nocturia and secondary nocturnal enuresis in children. Polydipsia develops in an attempt to maintain fluid balance. Insulin deficiency means that cells are unable to utilise glucose as fuel, therefore relying on lipolysis and proteolysis as an alternative fuel sources (12). Lipolysis, proteolysis and calorie loss from glycosuria lead to weight loss and hyperphagia (12). Other clinical features at presentation include increased urogenital infections such as urinary tract infections and candidiasis due to glycosuria (13).

Individuals can present at diagnosis in diabetic ketoacidosis (DKA) which is a life-threatening condition caused by a relative or absolute insulin deficiency, leading to lipolysis. The resulting free fatty acids are converted by the liver to ketones bodies (13). Once buffering capacity is exceeded for these acidic ketone bodies, acidosis ensues and symptoms develop, including vomiting and abdominal pain, in addition to the osmotic symptoms described above (14). A national survey revealed that 6.1% of admissions with DKA were people newly diagnosed with diabetes (15).

1.1.4 Management

T1D is managed with exogenous insulin given either as injections or a continuous subcutaneous infusion using a pump, to mimic physiological insulin secretion. A multiple daily injection regime (MDI) involves 1 or 2 doses of basal long-acting insulin along with boluses of short acting insulin to cover meals and snacks and as correction doses if hyperglycaemic. The majority of adults in England and Wales (82.3%) use MDI (16).

Commonly used basal insulins include Levemir (insulin detemir), Lantus (insulin glargine) and Tresiba (insulin degludec). Bolus insulins include Novorapid (insulin aspart) and Humalog (insulin lispro). Fiasp (fast-acting insulin aspart) is an example of an ultra-fast acting insulin analogue with added niacinamide to mediate faster initial absorption of insulin aspart (17). Its onset of action is faster than standard insulin aspart (- 4.9 minutes (-6.9 to -3.0 minutes); $p < 0.001$) (18). Within the first 30 minutes, the insulin exposure with fast acting insulin aspart is two times greater compared to insulin aspart (area under the curve (AUC) insulin aspart 0-30 minutes treatment ratio 2.01 95% CI (1.87-2.17); $p < 0.001$) and the early glucose lowering effect is 74% greater (AUC glucose infusion rate 0-30 minutes treatment ratio 1.74 (1.47-2.10; $p < 0.001$) (18). Lyumjev (ultrarapid lispro) is a further example of an ultra- fast acting insulin analogue with the excipients trepostinil (a prostacyclin analogue) and citrate, which have been shown in animal models to induce localised vasodilation and an increase in localised vascular permeability respectively, leading to accelerated insulin lispro absorption (19). A euglycaemic clamp study demonstrated a faster onset of action of ultra-rapid Lispro compared to Humalog (20 vs 31 min; $p = .0007$), greater early insulin lispro exposure (7.2 fold in first 15 minutes, 2.7 fold in first 30 minutes; both $p < 0.0001$) and shorter duration of action (20). The PRONTO-T1D randomised controlled trial showed that mealtime ultra-rapid lispro was superior to lispro

(Humalog) in reducing the postprandial glycaemic excursions during the liquid mixed meal tolerance test (estimated treatment difference -1.55 mmol/L 95% CI (-1.96 to -1.14) at 1 hour and -1.73 mmol/L 95% CI (-2.28 to -1.18) at 2 hours; both $p < 0.001$) (21).

Continuous subcutaneous insulin infusion (CSII), also known as an insulin pump, delivers short acting insulin all the time, with basal rates that can be adjusted in time blocks and boluses to cover meals and snacks. Several basal rate daily profiles can be set to accommodate differences in insulin sensitivity, for example at school or home for children and adolescents. Temporary basal rates allow flexibility to adjust the basal delivery by a set percentage, for example by increasing the basal rate when unwell or decreasing the basal rate during and after exercise. Pump boluses can be delivered as a standard bolus, an extended bolus over a longer period of time, for example with high fat foods or a buffet, or a combination bolus where a set percentage is given up front as a standard bolus and the rest as an extended bolus over a defined period of time, for example with high fat and high protein meals (22). Meta-analyses comparing CSII to MDI have found a lower glycated haemoglobin (HbA1c) (23, 24) with CSII, lower daily insulin requirements (24), a reduction in severe hypoglycaemia (25) or no significant difference in severe hypoglycaemia or nocturnal hypoglycaemia (23) and no significant difference in the rate of mild or overall hypoglycaemic events (24). However whilst some individuals report greater flexibility and freedom with pump therapy, some people find it has an impact on their body image and feelings of self- consciousness and social acceptance (26).

In addition, CSII is more expensive than MDI therapy and the REPOSE study found that CSII and the Dose Adjusted for Normal Eating (DAFNE) structured education course was not cost effective compared to MDI and DAFNE, adjusting for lower adverse event costs and

complication costs (27). The higher net incremental lifetime cost of pump vs MDI was estimated at £18,832 95% CI (£535-£34,978) with an increase in quality adjusted life years (QALY) of 0.126 95% CI (-0.738 to 0.97 QALYs) (27). Therefore the incremental cost-effectiveness ratio (ICER) associated with pump and DAFNE was £149,483 per QALY gained, which is above the threshold of £20,000-£30,000 that the National Institute for Clinical Excellence would usually consider to be cost effective (27). In participants with baseline HbA1c of at least 7.5% (58 mmol/L) , this study found a reduction in HbA1c in both the pump (mean (SD) -0.85% (1.25)%) and MDI arm (-0.42% (1.21)%) after 2 years but no difference in change in HbA1c between groups (-0.24%, 95% CI (-0.53 to 0.05%) in favour of the pump; p = 0.098). However there were a number of limitations with this study, for example participants were excluded if there were clear clinical indications for pump therapy as per the National Institute for Health Care and Excellence (NICE) guidance (28) or they expressed a keen preference for pump therapy (27), therefore possibly excluding those participants who could potentially gain the greatest clinical benefit from pump therapy. Each arm used different bolus calculators; participants in the pump arm used the Medtronic Bolus Wizard (Medtronic, Watford, UK) and participants in the MDI arm used the Accu-Chek Aviva Expert Bolus Advisor System (Roche Diagnostics Ltd, Burgess Hill, UK) (27). There was no information provided regarding changes to insulin doses prior to starting on a pump, the optimisation of settings or frequency of review of pump downloads (27, 29).

The REPOSE study results suggest that the initiation of pump therapy should be targeted to motivated individuals on MDI who are adjusting insulin doses following attendance at a structured education course but experiencing disabling hypoglycaemia or struggling to achieve their target HbA1c (27). This is in line with NICE technology appraisal guidance (28), which recommends CSII as an option for children aged 12 years or over and adults if efforts to achieve

target HbA1c have led to disabling hypoglycaemia or if their HbA1c has remained at a level of 69 mmol/mol (8.5%) or above on MDI despite a high level of care. For children under 12 years of age, CSII is recommended as an option if MDI is considered to be "inappropriate or impractical" and they are willing to go back on a trial of MDI between 12 and 18 years of age (28).

Glucose monitoring is used to aid insulin dosing decisions. Glucose monitoring includes self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM), divided into real-time continuous glucose monitoring (RT-CGM) and intermittently scanned continuous glucose monitoring (isCGM). SMBG involves fingerprick capillary blood glucose measurements whereas CGM measures the interstitial fluid levels using a sensor inserted through the subcutaneous tissue. The next section (1.2) compares these modalities and describes in detail the benefits and limitation of each. Glucose outcomes will be reported in international system (SI) units (mmol/L) for my own work and in SI or conventional units (mg/dL) for other studies, dependent on the units reported in the corresponding manuscript.

HbA1c is widely used to assess glycaemic control over the previous 8-12 weeks. HbA1c is a minor haemoglobin component in human erythrocytes, formed by the condensation of glucose to the N-terminal amino groups of the Hb A beta chains slowly over the 120 day erythrocyte life-span, probably by a non-enzymatic process (30). HbA1c results at 8 and 12 weeks have been shown to correlate closely with mean CGM glucose levels during the preceding 8 and 12 weeks (31) The principle value of HbA1c is in predicting the risk of development of complications. The Landmark Diabetes Control and Complications study demonstrated that participants in the intensive therapy group who adjusted insulin doses had a reduction in HbA1c

compared to the conventional therapy group, which was maintained from 3 months after baseline to the study end at 10 years (32). Intensive therapy compared to conventional therapy reduced the risk of developing retinopathy (adjusted mean risk reduction of 76% 95% CI (62-85%) ($p \leq 0.002$), developing microalbuminuria (mean adjusted risk reduction of 39% (21-52%); $p \leq 0.002$) and developing clinical neuropathy at 5 years (mean adjusted risk reduction of 60% (38-74%); $p \leq 0.002$) (32). HbA1c will be reported in both International Federation of Clinical Chemistry (IFCC) units (mmol/mol) and National Glycohaemoglobin Standardisation Programme (NSGP) units (%) for my own work and IFCC or NGSP units for other studies, dependent on the units reported in the corresponding manuscript.

Structured education programmes comprise trained educators following a fixed curriculum, in order to teach individuals how to self-manage their T1D more effectively (33). This includes a flexible approach to adjusting insulin doses around their lifestyle, including by counting carbohydrates, interpreting blood glucose values and accounting for factors which change insulin sensitivity, as previously described. The Diabetes Teaching and Treatment Programme (DTTP) is an early example of a structured education programme initiated in specialist diabetes centres in Dusseldorf/Vienna as a 5 day inpatient group teaching programme (34). A similar approach has been followed by the DAFNE study (35), delivered as a 5 day outpatient programme. These broad structured education programmes have been associated with an improvement in HbA1c (34-37) and reduction in severe hypoglycaemia (36, 37). There are also several structured education programmes focused on improving hypoglycaemia awareness, run as weekly sessions over a set time period (38-40), which have shown a reduction in moderate and severe hypoglycaemic events (38, 39) and an improvement in hypoglycaemia awareness (39, 40). These programmes are discussed in detail in section 1.3.4.

Sensor augmented pump (SAP) therapy integrates real-time continuous glucose monitoring (RT-CGM) with a pump with no automation of insulin delivery. A low glucose suspend algorithm pauses insulin delivery if sensor glucose levels fall to a set low threshold level. Predictive low glucose suspend (PLGS) pauses or reduces insulin delivery if the sensor glucose level is decreasing and is predicted to be below a defined low threshold within a set time period. A meta-analysis found that PLGS compared to SAP in children reduces the time spent in hypoglycaemia (<3.9 mmol/L; <70mg/dL) (absolute mean difference 17.4min/day 95% CI (-19.2 to -15.5 min/day)) and hypoglycaemia overnight (absolute mean difference 26.3 min/night (-35.5 to -16.7 min/day)), without increasing the percentage time above range or episodes of DKA (41). A meta-analysis of randomised controlled cross-over studies (n=4) using PLGS and non-PLGS periods found that based on the pooled estimate, PLGS overnight periods were associated with a 8.8% lower risk of hypoglycaemia (risk difference -0.088 95% CI -0.119 to -0.056) (42).

Hybrid closed loop (HCL) systems incorporate PLGS, but in addition also adjust insulin delivery if the sensor glucose level is above target glucose, by increasing the basal rate and/or micro-correction boluses. However, individuals are still required to give manual insulin boluses with meals. Commercially available HCL systems in the UK include the Medtronic 670g with Guardian 3 sensor and 780g with Guardian 4 sensor, the Control IQ system (T-slim pump with Dexcom G6) (Tandem, CA, USA) and the CamAPS FX (Dana pump with Dexcom G6) (Cam Diab, Cambridge, UK) (43). HCL systems are also known as artificial pancreas (AP) systems. Single hormone AP systems use exclusively insulin whereas dual hormone AP system use both insulin and glucagon. A meta-analysis of AP systems found in a sub-analysis of single hormone AP systems compared to control (SAP in most studies) an increase in time in range (3.9-10.0 mmol/L) (+ 8.5% (95%CI 6.3 to 10.7)% over 24 hours and 12.8% (9.8-15.7%)

overnight), reduction in time above range over 24 hours (>10 mmol/L) (-7.5 (-10.4 to -4.7)%) and reduction in time below range (<3.9 mmol/L) (-1.3 (-1.7 to -0.9)% over 24 hours and -1.8 (-2.4 to -1.3)% overnight (44). The psychosocial impact of HCL includes benefits such as decreased anxiety, better sleep and some breaks in dealing with the constant demand of diabetes self-management but also challenges such as technical issues and difficulty trusting the system (45). Draft NICE HCL guidance published in January 2023 (46) recommends HCL systems as an option for individuals who are finding T1D self-management challenging and have a HbA1c of around 64 mmol/mol (8%) or above, despite optimal treatment with at least one of CSII, RT-CGM or isCGM, provided that individuals or their carer understand how the system works and are undertaking a structured education programme. A comprehensive review of insulin pump therapy and automated insulin delivery is beyond the scope of this thesis.

1.1.5 Association of ethnicity and deprivation with glycaemic outcomes and uptake of technology

It is recognised that there are differences in glycaemic control and complication rates in T1D across ethnic and racial groups and social-economic status, which may be in part due to inequity of access to diabetes technology (21, 47-49). The Type 1 Diabetes Exchange (T1DX) Quality Improvement Collaborative of 34 U.S. diabetes clinics (n= 19,226 children and adults) found that both HbA1c (adjusted for age and insurance status) and the rates of acute complications were significantly different across racial/ethnic groups (both $p < 0.001$) (47). Non-Hispanic Black individuals had the highest mean HbA1c (10.3%) and highest rates of severe hypoglycaemia (5.1% reporting at least one event over the study period of nearly 3 years) and DKA (28%) (47). There is a disparity in diabetes technology use, with non-Hispanic Black individuals having the lowest rates of both CGM (17%) and insulin pump use (41%)

(47). Similar results were found specifically in young adults in the T1DX registry, with a disparity in HbA1c between non-Hispanic Black young adults and non-Hispanic White young adults of 2.26% (95% CI 1.46 – 3.07%) ($p < 0.001$) (48). A significant proportion of this HbA1c disparity was explained by socio-economic status, diabetes technology use, diabetes distress and diabetes self-management (48). For children <18 years of age, international registry data from the T1DX and the Diabetes Prospective follow up registry (DPV, Germany) have shown a higher HbA1c in children with lower socio-economic status (SES) (49). The disparities in HbA1c by SES have increased significantly for children in the T1DX registry from 2010-2012 to 2016-2018 ($p<0.0001$) (49); however this increase is no longer significant after adjusting for diabetes technology use (49). Whilst a causal relationship cannot be conferred, there is a growing body of real-world evidence that diabetes technology use is associated with improved glycaemic outcomes (50-52).

The National Type 1 Diabetes Audit in England and Wales 2020-2021 (53) found that being of Black or mixed ethnicity and living in a more deprived area were characteristics associated with an increased likelihood of having an HbA1c of 86 mmol/L or higher and a decreased likelihood of having an HbA1c of 58 mmol/L or lower. The National Type 1 Diabetes Audit demonstrated a disparity in both technology use and attendance at structured education courses across ethnic and racial groups and quintiles of deprivation (53). The use of CGM and an insulin pump were more prevalent in individuals who were younger, of White ethnicity and living in the least deprived areas (53). Insulin pump use was less common in individuals who were older, of Black or Asian ethnicity and living in more deprived areas (54). People who were White and living in the least deprived areas attended structured education courses more commonly (53).

Reducing these health inequities is of upmost importance. Universal state funding may reduce the impact of socio-economic status on diabetes technology uptake. The Australian government introduced universal fully subsidised CGM for individuals <21 years of age who met the eligibility criteria in 2017, leading to an increase in CGM uptake from 5% to 79% after 2 years and associated with a sustained improvement in glycaemic control, with an odds ratio of achieving the HbA1c target of <7% at 12 months of 2.5 (95% CI 2.1 to 2.9) ($p < 0.001$) and at 24 months of 2.3 (1.9 to 2.8) ($p < 0.001$). However, there are disparities in glycaemic control and technology uptake in the U.K. despite universal state funding. This highlights that there are a number of additional barriers which need to be explored in order to increase technology uptake in diverse ethnic and racial groups and reduce health inequities. The T1D Exchange QI collaborative are undertaking a range of key interventions to reduce inequities, such as addressing provider implicit bias, focusing on patient involvement and benchmarking performance (55). Twice yearly benchmarking of 22 centres in 19 countries within the "Better Control in Paediatric and Adolescent Diabetes: working to Create Centres of Reference" (SWEET) registry over 10 years and centres collaborating to share learning and knowledge, has been associated with a significantly improved HbA1c on a background of increasing pump and sensor use (51).

1.2 Glucose monitoring

1.2.1 Self-monitoring of blood glucose levels

SMBG involves a fingerprick to draw capillary blood which is then placed onto a test strip**.** The enzyme glucose oxidase on the working electrode oxidises the glucose to produce an amount of current and subsequently voltage proportional to the glucose level, via the current-to-voltage converter in the meter (56). Disadvantages of SMBG include only providing a snap shot of the glucose level at that precise moment in time, with no information about the rate of change, trend or glucose levels in between measurements. Finger injury (haematoma, induration, ketosis or scarring) is associated with the frequency of fingerpricking (57). SMBG can be painful (57) and inconvenient, requiring individuals to carry SMBG equipment out with them and interrupting their activities (58). Le FLoch et al (57) observed that best practice guidance was often not followed, including by educated patients who were followed up, for example 30% never changed the fingerprick site, 29% always reused the lancet and 30% did not wash their hands beforehand. One advantage of SMBG is lower cost than RT-CGM and isCGM (59, 60) and greater accuracy. One study investigating the accuracy of blood glucose meter readings found that 6 out of the 7 tested meters had 100% of blood glucose measurement results falling within zones A and B on the Clarke Error Grid Analysis (61), considered clinically accurate or benign (62). SMBG measures the glucose level in capillary blood compared to CGM which measures glucose level in the interstitial fluid and these are similar for steady state conditions only; the accuracy of CGM systems are usually determined by comparing matched sensor glucose measurements to SMBG glucose measurements (63). Further details are provided in the next section (1.2.2).

1.2.2 Continuous glucose monitoring

CGM comprises three components; a sensor, transmitter and receiver (56, 64); the sensor is a very small probe inserted through the subcutaneous tissue to measure the glucose level in the interstitial fluid (ISF) and uses the enzyme glucose oxidase to convert glucose in the ISF to hydrogen peroxidase, which reacts with platinum to generate an electrical current proportional to the glucose level (56, 64). The current travels along the wire to the transmitter, which sits on the outside of the skin and sends a signal to the receiver which calculates and displays the glucose level (56). The rate of change of glucose level is represented by an arrow. Sensors usually measure glucose levels every 1 to 15 minutes, with some CGM systems requiring calibration by the user by manually entering capillary blood glucose values every 12-24 hours, whereas other CGM systems are licenced for use without routine calibration (64).

CGM confers additional benefits over HbA1c in the assessment of glycaemic control. It provides information about glycaemic variability, patterns of hypo- and hyperglycaemia, glycaemic excursions and daily profiles which can be used to guide therapeutic changes (65). It is also not affected by conditions such as iron deficiency, haemolytic anaemia or haemoglobinopathies which can impact the sensitivity and specificity of HbA1c (66). International consensus guidance (65) on CGM metrics have been published which include targets for time in range (TIR), time below range (TBR) and time above range (TAR) (table 1).

	Percentage of readings	Time per day
Time in range: 3.9-10.0 mmol/L (70- 180mg/dL)	>70%	>16hours, 48 minutes
Time below range: <3.9 mmol/L (<70mg/dL) <3.0 mmol/L (<54 mg/dL)	 < 4% <1%	 <1 hour <15 minutes
Time above range: >10.0 mmol/L (>180mg/dL) > 13.9 mmol/L (>250mg/dL)	 <25% <5%	 <6 hours <1 hour 12 minutes

Table 1.1: International consensus guidance on targets for assessment of glycaemic control in adults with T1D* (65)

*This does not include older or high-risk adults with T1D or pregnant women with T1D. There are different targets for these groups (65).

The accuracy of CGM can be assessed by the mean absolute relative difference (MARD). MARD is the average absolute difference between CGM readings and comparison glucose values, which can be either capillary blood glucose measurements or venous blood glucose values as analysed by the Yellow Springs Instrument (YSI) (63). A CGM system MARD of less than 10% has been estimated in silico to be an acceptable degree of accuracy in order to make treatment decisions without requiring confirmatory finger prick glucose values (non-adjunct CGM use) (67).

There are two categories of continuous glucose monitoring; real-time continuous glucose monitoring (RT-CGM) and intermittently-scanned continuous glucose monitoring (isCGM) (Table 2). Glucose values are transmitted automatically from the sensor to a reader or smartphone application with RT-CGM, whereas glucose readings are only displayed when the sensor is scanned with a reader or smartphone application with isCGM. Table 2 compares the commercially available RT-CGM and isCGM devices in the UK.

	Dexcom G6	Dexcom G7	Medtrum Touchcare Nano	Medtronic Guardian sensor 3 (Guardian connect system)	Medtronic Guardian sensor 4	Freestyle Libre 2	Freestyle Libre 3
Glucose readings	Transmitter automatically sends glucose readings every 5 minutes to smartphone or reader (transmitter stores 3 hours of data)	Transmitter automatically sends glucose readings every 5 minutes to smartphone or reader stores (transmitter stores 24 hours of data (68))	Transmitter automatically sends glucose readings every 2 minutes to smartphone	Transmitter automatically sends glucose readings every 5 minutes to smartphone	Transmitter automatically sends glucose readings every 5 minutes to smartphone	Displayed when scan sensor with reader or smartphone application. Stores 8 hours of glucose data displayed at 15 minute intervals	Sensor transmits glucose levels every minute to smartphone.
Sensor life	Up to 10 days	Up to 10.5 days (12 hour grace period to change sensor) (68)	Up to 14 days	Up to 7 days	7 days	Up to 14 days	Up to 14 days
Routine calibration required	No	No	No	Yes (≥ 2 times/day)	No	No	No
Warm up period	2 hours	27 minutes (68)	1 hour	Up to 2 hours	2 hours	1 hour	1 hour
Transmitter life	3 months	10.5 days (integrated sensor and transmitter)	Rechargeable transmitter (on 1st use charge for up to 2 hours, subsequent charges 10-30 minutes)	Transmitter requires charging (takes up to 2 hours, fully charged lasts ≥ 7 days	Transmitter requires charging (fully charged lasts ≥ 7 days)	N/A	N/A
Water resistant	Waterproof at depth of 2.4 metres for up to 24 hours (69)	Waterproof at depth of 2.4 metres for up to 24 hours (69)	Waterproof at depth of 2.5 metres for up to 1 hour	Waterproof to 2.4 metres for up to 30 minutes	Waterproof to 2.4 metres for up to 30 minutes	In up to 1 metre of water for a maximum of 30 minutes	In up to 1 metre of water for a maximum of 30 minutes
Alarms/alerts	Urgent low* (mandatory) Urgent low soon ** (optional) Low (optional) High (optional) Rise/fall rate (optional) (70)	Urgent low* (mandatory) Urgent low soon ** Low (optional) High (optional) Rise/fall rate (optional) Delay 1st alert (high alert) (71) Quiet mode (silence all alerts for up to 6 hours) (71)	High/low alerts (personalise) Predictive high and low alerts/alarms to provide up to 20 minutes advance warning	Urgent low SG alert (≤ 55mg/dL) (mandatory unless alerts disabled) Low/high limit alerts (personalisable) Predictive high/low glucose alerts up to 60	High SG alert set at ≥13.9 mmol/L for 3 hours (fixed) Low SG alert set at ≤ 3.0 mmol/L (fixed) Low/high limit alerts (personalisable) Predictive high/low glucose alerts Rise alert	Optional low and high alerts (personalisable)	Optional high and low alerts (personalisable)

				minutes in advance Rise/fall alert			
Overall MARD	Adults: 9.8% (abdomen placed) (72) Paediatrics (abdomen or upper buttock placed): 7.7% (72) (Within CGM reportable range 40-400mg/dL)	Adults: 8.2% (arm placed), 9,1% (abdomen placed) (73) (Within CGM reportable range 40-400mg/dL)	No published data (data "on file" shared for review paper (74) MARD 9.7% in adults ***)	Calibration every 12 hours: 10.6%/10.4% (abdomen placed with 640G pump/Guardian connect respectively), 9.1% (arm placed). Calibration 3-4 times/day: 9.6%/9.4% (abdomen placed with 640G pump/Guardian connect respectively), 8.7% (arm placed) (75)	No published data (data on file for MARD included in review paper (74) when used with Guardian Link 4 transmitter Children 11.6-12.3% Adults 10.6-10.8%****)	Adults: 9.2% Children (6-17 years of age): 9.7% (76) (for sensor results within reportable range of 40-500mg/dL)	Adults 7.6% Children (6-17 years of age) 8.7% (77)
Approved sensor sites	≥18 years: abdomen or back of upper arm Upper buttocks (children only aged 2-17 years) (69)	≥18 years: abdomen or back of upper arm Upper buttocks (children only aged 2-6 years) (69)	Upper arm	Abdomen or back of upper arms	7-17 years: upper buttocks or back of upper arm ≥18 years: back of upper arm or abdomen	Back of upper arms	Back of upper arms
Pump compatibility	Tandem T:slim CamsAPS FX(69) Omnipod 5 (FDA approved)	-	Medtrum tubeless insulin pump	Minimed 640G and 670G	Minimed 780G	No	Ypsomed pump and CAM-APS FX (HCL system available in Germany)
Sharing function	Follow app- circle of support (max 10) (69)	Follow app- circle of support (max 10) (69)	Yes	Yes (Carelink)	Yes	Yes	Yes

Table 1.2: Comparisons between CGM systems commercially available in the U.K.

Dexcom G6 (68-70, 72), Dexcom G7 (68, 69, 71, 73), Medtrum Touchcare Nano (78, 79), Medtronic Sensor Guardian 3 (80), Medtronic sensor Guardian 4 (81, 82), Freestyle Libre 2 system (83) and Freestyle Libre 3 system (84).

Abbreviations: Mean absolute relative difference (MARD); sensor glucose (SG)

*Urgent low alert: mandatory and fixed threshold of ≤3.1 mmol/L (70, 71)

**Predictive alert when blood glucose forecasted to be ≤3.1 mmol/L within 20 minutes (70, 71)

***data on file and permission granted to share for review article by Pemberton et al (74) n=61, ≥14 years of age. Authors note limitations to the data on file such as assessing accuracy on less than 40% of days of sensor life may not be representative of accuracy across entire sensor life and the paucity of accuracy measure reported.

**** Data on file for MARD when used with Guardian Link 4 transmitter included in review article by Pemberton et al (74).

RT-CGM and isCGM are explored in more detail below, including their indications for use and their effectiveness compared to alternative methods of glucose monitoring.

1.2.3 Real-time continuous glucose monitoring

The transmitter in real-time continuous glucose monitoring systems sends glucose readings to a reader or smartphone every 2 to 5 minutes automatically with alarms/alerts for hypoglycaemia, hyperglycaemia, hypoglycaemia prediction and glucose rate of change (64).

Guidance by the London Diabetes Clinical Network and National Health Service (NHS) London Procurement partnership in 2018 for the commissioning and provision of RT-CGM in adults with T1D focused on problematic hypoglycaemia (85). It was limited to individuals who had a history of more than one severe episode of hypoglycaemia with no obvious avoidable cause within a year, individuals who had complete hypoglycaemia unawareness, at least 2 episodes a week of asymptomatic hypoglycaemia interfering with daily activities, extreme fear of hypoglycaemia or inability to achieve a HbA1c of 75mmol/mol (9%) despite SMBG at least 10 times/day (85). These were based on the NICE guidance at the time (NG17) (86), which has been since been updated in 2022 (87) to offer adults with T1D a choice of RT-CGM or isCGM, taking into account a range of factors, including their individual needs, for example related to hypoglycaemia awareness and severity, their individual characteristics and preferences, for example in regards to their occupation, and the device capability, for example compatibility with an insulin pump and data sharing functionality.

A large meta-analysis (n = 21 studies, n = 2149 participants) showed that RT-CGM was associated with a greater reduction in HbA1c compared to SMBG, with the greatest benefit

observed in those with a baseline HbA1c > 64 mmol/mol (>8.0%) (88). A number of randomised controlled studies have compared RT-CGM to SMBG in terms of glycaemic outcomes, demonstrating a reduction in HbA1c (89-94), less time spent in hypoglycaemia (89, 91, 95, 96) and fewer episodes of severe hypoglycaemia (91, 96). These have been in heterogenous study populations; adults specifically on MDI (89, 93), adults with impaired awareness of hypoglycaemia (95, 96) or an episode of recent severe hypoglycaemia (95), combined study populations of adults and children (90, 94, 97) , adolescents and young people (92, 98) or older participants at least 60 years old (91, 99). The next section will explore the evidence for these population subgroups.

Adults specifically on Multiple Daily Injections of insulin

Studies in adults specifically on MDI have demonstrated a greater reduction in HbA1c with RT-CGM compared to SMBG (89, 93) and an improvement in glycaemic outcomes (89). The GOLD study was a randomised controlled crossover study, demonstrating a lower HbA1c during CGM use than during conventional treatment with SMBG (mean difference -0.43% (95% CI -0.57 to -0.29%); $p < 0.001$)(93). The DIAMOND study found a greater reduction in HbA1c from baseline in the CGM group compared to the control group (SMBG) (mean adjusted between group difference -0.6% (95% CI (-0.8 to -0.3), $p < 0.001$) (89). TBR < 70mg/dL was lower in the CGM group compared to the control group (median 43 min/day (IQR 27-69) versus 80 min/day (36-111); $p = 0.002$) (89). There were no statistical tests for comparison of percentage TBR between groups reported for the GOLD study (93).

Adults with impaired awareness of hypoglycaemia or recent severe hypoglycaemia

The HypoDe study (95) and IN CONTROL study (96) investigated adults with impaired awareness of hypoglycaemia (95, 96) or a history of severe hypoglycaemia within the preceding year (95), finding that RT-CGM reduces percentage TBR (95, 96), the number of hypoglycaemic events (95) and the number of severe hypoglycaemic events (96). In terms of the possible mechanistic explanations, the HypoDe study observed that whilst participants in the RT-CGM group did not make any major adjustments to insulin therapy, they were more pro-active at preventing hypoglycaemia, by increasing their intake of rescue carbohydrates and consuming these at a higher glucose level threshold (100). The IN CONTROL study demonstrated that emotional wellbeing, diabetes related distress and fear of hypoglycaemia did not appear to modify the impact of RT-CGM on glycaemic outcomes (101).

The RT-CGM alarms appear to have an influence on TBR, with the GLADIS study (n=160 on MDI/CSII, 86.9% T1D) observing a reduction in TBR (<3.9 mmol/L (<70mg/dL)) in the RT-CGM group with alarms compared to SMBG (1.0 versus 1.6 hours/day; 95% CI for difference -1.2 to -0.1; p = 0.03) but no difference found in the RT-CGM group without alarms compared to SBMG (1.3 versus 1.6 h/day; 95% CI for difference -0.8 to 0.3; p = 0.35) (102). Hypoglycaemia alerts were used in the RT-CGM arms of the HypoDE (95) and IN CONTROL (96) studies described above which demonstrated a reduction in percentage TBR.

Combined study populations of adults and children

Controlled studies in combined study populations of adults and children have found a reduction in HbA1c compared to SMBG (90, 94). Battelino et al (n= 120) demonstrated that there is a benefit to using RT-CGM in individuals with well controlled diabetes (baseline HbA1c <7.5%)

on MDI/CSII, finding favourable results compared to SMBG; a greater reduction in HbA1c (HbA1c difference at 26 weeks -0.27% (95% CI) -0.47 to -0.07; p = 0.008), greater TIR (70-180mg/dL) (mean 17.6 ± 3.2 vs 16.0 ± 3.4 hours/day; p = 0.009) and lower TAR > 180mg/dL (mean 5.5 ± 3.2 versus 6.4 ± 3.4 hours/day; p = 0.08) (90). Similar improvements in glycaemic outcomes were shown in the Juvenile Research Foundation Study group but only in those ≥ 25 years of age (mean (SD) HbA1c 7.6% (+/-0.5)) (97) and not in the younger age groups. One possible explanation for this could be that a higher proportion of participants in the ≥25 years age group wore CGM for ≥6.0 days per week (83%) compared to in the younger age groups (30% of 15-24 year olds, 50% of 8-14 year olds) (97). Riveline et al demonstrated that RT-CGM use in individuals with suboptimal glycaemic control (HbA1c ≥8.0%) was associated with an improvement in HbA1c compared to SMBG, whether prescribed for continuous use (patient led) or intermittently (physician led) with the frequency of use based on glycaemic outcomes (94) (patient led CGM vs SMBG - 0.52%; p =0.0006) (physician led CGM versus SMBG -0.47%; p = 0.0008). This benefit was observed in CSII users and not MDI users (94).

Studies in adolescents and young people

Studies specifically in adolescents and young people have found a greater HbA1c reduction, greater TIR (70-180mg/dL) and lower TAR (> 180 and 300 mg/dL) with RT-CGM compared to SMBG (92, 98). The MILLENNIALS study found percentage TBR <70 mg/dL low and comparable in both groups (median (IQR) CGM 1.45 (0.40-4.08)% versus SMBG 0.58 (0.20-3.50)%; p = 0.055) (92) whereas the CITY study showed it was significantly lower in the RT-CGM group (CGM 2.2 (1.0 to 5.0)% versus SMBG 3.2 (1.9 to 6.2)%; adjusted between group difference -0.7% (95% CI -1.5 to -0.1%); p= 0.02) (98). A possible explanation for this difference could be due to the different study designs and duration of intervention; the CITY

study (98) was a longer parallel randomised controlled trial (RCT) over 26 weeks compared to the MILLENNIALS study (92) which was a randomised crossover study with only 8 weeks in each phase. The longer duration of the intervention arm in the CITY study may have allowed more time for a beneficial treatment effect to be seen.

Studies in older participants

Two studies have compared RT-CGM to SMBG in older participants of at least 60 years of age over a 24 or 26 week period, demonstrating improved TIR (70-180mg/dL), lower TAR (>250 mg/dL) and a greater reduction in HbA1c with RT-CGM (91, 99). The WISDM study in participants with T1D (n = 203) also demonstrated a reduction in percentage TBR <70mg/dL (median (IQR) CGM 2.7 (1.6-4.6)% versus SMBG 4.9 (2.5-8.5)%; adjusted difference CGM-SMBG -1.9 (95% CI -2.8 to -1.1); p < 0.001))(91) which was sustained over the 26 week extension period (103). WISDM results also showed a lower percentage TBR <60mg/dL with CGM compared to SMBG (CGM 0.9 (0.5-1.9)% versus SMBG 2.4 (0.8-5.1)%; adjusted difference -1.4 (95% CI -2.0 to -0.8); p< 0.001) (91). A difference in percentage TBR <60mg/dL was not observed in the subset of the DIAMOND study (n =116) (99); however the majority had type 2 diabetes (70.7%) and participants had low baseline TBR <60mg/dL (median (IQR) CGM 10 (1- 38) versus SMBG (8 (1- 23) minutes/day) (99). This is in comparison to the higher baseline median TBR <60mg/dL in the WISDM study of 3.0% in CGM group (equivalent to 43 minutes/day) and 2.4% in SMBG group (equivalent to 35 minutes/day) (91). It is recognised that older people with T1D are at increased risk of severe hypoglycaemia (104). Recent severe hypoglycaemic events (≥2 in the last year) and hypoglycaemia unawareness are associated with increased odds of clinically significant cognitive impairment (105). This highlights the potential impact of RT-CGM in an older

population, which has been found to reduce the risk of severe hypoglycaemia (91). In the WISDM study, there were 10 severe hypoglycaemia episodes in the SMBG group compared to one in the RT-CGM group, (incident rate per 100-person years 1.9 CGM versus 22.4 SMBG, difference -20.4 (95% CI (-34.6 to -6.3)); p = 0.02) (91).

Impact of real-time continuous glucose monitoring on diabetes specific quality of life and overall health and wellbeing

Studies have shown a beneficial or equivocal effect of RT-CGM compared to SMBG in terms of diabetes specific quality of life outcomes and overall health and wellbeing as measured by standardised questionnaires (93, 94, 106-108). In terms of diabetes specific outcomes, RT-CGM is associated with a greater decrease in diabetes distress (107), greater treatment satisfaction (93), no change in hypoglycaemia fear (107) but a greater increase in hypoglycaemia confidence (107). The GOLD study found that RT-CGM compared to SMBG was associated with greater confidence in being able to avoid serious problems due to hypoglycaemia, in continuing to do activities as they wish despite the risk of hypoglycaemia and in detecting and responding to blood glucose levels before they drop too low (106). The Juvenile Diabetes Research Foundation (JDRF) study found an slight improvement in hypoglycaemia fear survey total score and behaviour subscale scores with RT-CGM compared to SMBG in adults (108).

RT-CGM is associated with a variable impact on general health and wellbeing. Studies have shown higher overall wellbeing scores (93) as measured on World Health Organisation 5 (WHO-5) wellbeing index (109); no difference in wellbeing scores (107); no difference in

health status scores (107) or an improvement in physical health scores but with no difference in overall quality of life scores (94).

Cost-effectiveness

Whilst it has been demonstrated that RT-CGM is associated with an improvement in glycaemic outcomes (89-96) and some quality of life outcomes (93, 107), the decisions around public funding are largely based on cost effectiveness. RT-CGM has been shown to likely be cost effective, in view of improved glycaemic control and quality of life benefit gained from reduced fear of hypoglycaemia and fingerprick testing (59, 60, 110). Modelling studies in Australia, France and the U.K. using clinical input data from the DIAMOND study (89, 107, 111), found Dexcom G6 (Dexcom Inc., San Diego, CA, USA) is associated with an incremental gain in quality adjusted life years (QALY) of 1.20 (60), 1.38 (110) and 1.49 (59) respectively, compared to SMBG in people with T1D. The incremental cost effective ratio (ICER) was then calculated by dividing the increase in total lifetime costs of RT-CGM compared to SMBG by QALY gained and was found to be lower than the commonly referenced willingness to pay threshold per QALY gained (59, 60, 110). Conversely, another cost effective analysis found that the ICERs per QALY were higher than the estimated threshold in Spain and therefore concluded that RT-CGM was not cost effective (112). However this analysis investigated RT-CGM use compared to SMBG in type 2 diabetes in addition to T1D (112). Additionally, the systematic review and meta-analysis used to assess the effectiveness of RT-CGM focused exclusively on HbA1c and rates of severe hypoglycaemia as outcomes (112), without assessment of non-severe hypoglycaemia or impact on patient reported outcomes such as fear of hypoglycaemia, which were taken into account in the previously described cost-effective analyses (59, 60, 110).

Barriers to real-time continuous glucose monitoring use

Whilst international consensus recommendations are that CGM is active for ≥ 70% of the time (65) and it is recognised that RT-CGM has a greater benefit in those who use it most frequently (113), evidence suggests that there are barriers to achieving this. In the pivotal JDRF study (97), there was no change in HbA1c for adolescents and young adults (8-14 years of age mean difference -0.13 (95% CI -0.38 to 0.11; p = 0.29) (15-24 years of age mean difference 0.08 (95% CI -0.17 to 0.33; p = 0.52), who wore it for less time than adults and these groups wore it less frequently as the study progressed (97).

Both parents of young children with T1D (n = 55) (114) and adults with T1D (n =23) (115) have described the following barriers; painful insertion, skin irritation or adhesive issues and an overwhelming amount of information which is challenging to interpret. Whilst adults reported that wearing the sensor drew attention to their diabetes and could lead to body image issues (115), parents were concerned about the space available on small bodies to place multiple devices (114) whilst also wearing an insulin pump. Some people find the alarms disruptive (114, 116). Technical issues reported include signal loss (114), sensor inaccuracy and unreliability (116), the sensor lifetime being shorter than expected (116) and the lag time (115, 116). CGM readings measure interstitial fluid glucose levels rather than blood glucose levels and this lag in readings can be particularly pronounced during prolonged aerobic exercise, with the CGM fall in glucose levels found to lag behind the fall in blood glucose levels by 12 +/- 11 minutes in one small study (n = 17) (117).

Whilst downloading data can help individuals identify patterns and make changes to insulin regimes, evidence suggests that many individuals prefer to use the real-time data provided by

CGM (118). A survey of 17,317 children and adults with diabetes in 2014 enrolled in the T1D Exchange Registry found that 9% use CGM, of whom 27% downloaded their data once a month and less than 15% downloaded their data at least weekly (118), reporting that retrospective data analysis was deemed to be the least useful feature and preferring to use the real time features, such as the arrows demonstrating the rate of change. Qualitative interviews with adults reported similar findings, with no participants downloading CGM data themselves and some preferring to review retrospective data downloads with their diabetes health care professional (115).

Summary

In summary, RT-CGM is associated with an improvement in glycaemic outcomes compared to SMBG in a variety of study populations (89-96), an improvement in some quality of life outcomes (93, 107) and is likely cost effective (59, 60, 110). Whilst it has a greater benefit for those who use it most frequently (113), there are barriers to individuals using it including technical issues, sensor issues, disruptive alarms and an overwhelming amount of information (114-116).

1.2.4 Intermittently scanned continuous glucose monitoring

The Freestyle Libre (Abbott Diabetes Care, Almeda, CA, USA) isCGM device includes a sensor which is worn on the back of the arm and lasts up to 14 days (119). When the sensor is scanned with a reader or the smartphone application, the glucose readings over the previous 8 hours are displayed in 15 minute intervals (119). The Freestyle Libre has an 8 hour memory; if not scanned within this time period then data is lost (64). The Freestyle Libre does not have

any alerts or alarms (64). The Freestyle Libre 2 (Abbott Diabetes Care, Almeda, CA, USA) has optional high and low alerts (83).

Intermittently scanned continuous glucose monitoring compared to self-monitoring of blood glucose

Studies comparing isCGM to SMBG suggest that there is no difference in HbA1c change between groups (120, 121). In adults with well controlled T1D (HbA1c <7.5%) and intact awareness of hypoglycaemia (n= 241), the Freestyle Libre was associated with a 38% reduction in time in hypoglycaemia (<3.9mmol/L; < 70 mg/dL) in the intervention group compared to control (SMBG) group (mean (SD) 2.03 (1.93) intervention versus 3.27 (2.58) h/24h period control; between group difference -1.24 (SE 0.239); p< 0.001)(120). There was no difference in HbA1c at study end between the groups (52.4 (7.2) mmol/mol intervention versus 52.4 (7.2) mmol/mol control; p = 0.96) (120). Similar results were found specifically in the MDI sub-analysis (n = 167) in terms of TBR < 70mg/dL (mean (SD) 1.86 (1.36) intervention versus 3.66 (2.79) h/24h period control; between group difference -1.65 (95% CI -2.21 to -1.09) p < 0.0001) and HbA1c (53.0 (6.5) mmol/mol intervention versus 52.0 (7.5) mmol/mol control; p = 0.77) (121). In a different study population of adolescents with suboptimal glycaemic control (baseline HbA1c >75 mmol/mol) (>9.0%)), there was no difference in change in HbA1c found between isCGM (Freestyle Libre) and SMBG at 6 months compared to baseline (mean ± SD baseline intervention 94.0 ± 18.0 mmol/mol versus control 98.8 ± 17.8 mmol/mol; 6 months intervention 86.1 ± 16.5 mmol/mol versus control 93.2 ± 15.9 mmol/mol; difference in adjusted changes at 6 months -2.1 mmol/mol (95% CI -9.6 to 5.4); p =0.576) (122). This was despite higher glucose monitoring frequency (baseline intervention (interstitial and capillary) 1.8 ± 1.6 versus control (capillary) 1.9 ± 3.6; 6 months intervention 3.8 ± 3.1 versus control

1.4 ± 3.0; difference in adjusted changes at 6 months 2.8 (1.72-4.65); p < 0.001) (122). Other glycaemic outcomes were not reported; the control group did not wear blinded isCGM at any point (122).

Data suggests that the addition of optional high and low alerts in the Freestyle Libre 2 is associated with a greater impact on glycaemic outcomes (123). In a study population (≥ 16 years of age) with baseline mean HbA1c (± SD) 8.6% (± 0.8%) (n =156), the Freestyle Libre 2 was associated with a greater reduction in HbA1c than SMBG (adjusted mean between group difference -0.5 %; 95% CI -0.7 to -0.3; p < 0.001) (123). The Freestyle Libre 2 group also had a reduction in percentage time spent in hypoglycaemia (<70mg/dL) (adjusted mean difference -3.0 (95% CI -4.5 to -1.4) and hyperglycaemia (>180mg/dL) (adjusted mean difference -6.0 (-11.0 to -0.9) and an increase in percentage time spent in target range (70-180mg/dL) (adjusted mean difference 9.0 (4.7-13.3) (only CIs reported, no p values) (123).

Intermittently scanned continuous glucose monitoring compared to real-time continuous glucose monitoring

There are several published studies published comparing isCGM (Freestyle Libre) to RT-CGM, demonstrating more favourable glycaemic outcomes with RT-CGM, including improvement in percentage TBR (124-126) and percentage TIR (125-127). In adults with impaired awareness of hypoglycaemia (GOLD≥4) or a history of severe hypoglycaemia within the previous 12 months, 8 week use of RT-CGM led to a greater reduction in percentage TBR from baseline at all thresholds (<2.8 mmol/L; <3.3 mmol/L; <3.5 mmol/L; <3.9 mmol/L) compared to isCGM (p values all < 0.05). For example the median change from baseline in percentage TBR <3.3 mmol/L as the primary outcome was -3.0 (95% CI -5.0 to -0.3) with

CGM compared to 1.3 (-1.4 to 3.6) with isCGM; p = 0.006 (124). Similar results were found for specifically the overnight period (22:00-07:00) (124). Whilst there was no difference in HbA1c change between groups in this study (124), other studies of longer duration have demonstrated a more favourable impact on HbA1c with RT-CGM compared to isCGM (126, 127), including specifically in MDI users (126). The CORRIDA study in adults with hypoglycaemia awareness (GOLD <4) and no history of severe hypoglycaemia within the last 6 months, found during both the exercise (4 days) and home (4 weeks) phases, an increase in percentage TIR (3.9-10 mmol/L) with RT-CGM compared to isCGM (exercise 78.5 ± 10.2% versus 69.7 ± 16%; p = 0.0149) (home 75.6 ± 9.7% versus 67.4 ± 17.8%; p = 0.0339) and a reduction in percentage TBR <3.9 mmol/L (exercise 6.8 ± 5.5% versus 11.4 ± 8.6%; p = 0.018) (home 5.3 ± 2.5% versus 7.3 ± 4.4%; p = 0.035)(125). Whilst other studies excluded participants who had used RT-CGM or isCGM recently (124-126), the ALERTT1D study included adults who had used isCGM exclusively for the last 6 months (n = 254) with the majority using MDI (81%), showing that switching to RT-CGM (intervention) for 6 months compared to the isCGM (control) group was associated with a higher percentage TIR (3.9-10.0 mmol/L) (mean 59.6% versus 51.9%; mean difference 6.85 percentage points (95% CI 5.46-9.34); p< 0.0001), lower percentage TBR < 3.0 mmol/L (0.47% versus 0.84%;-0.35 percentage points (-0.61 to -0.10) p =0.007) and fewer episodes of severe hypoglycaemia (n = 3 vs n =13; p = 0.0082)(127). A real-world retrospective observational study with matched RT-CGM and isCGM cohorts (n = 143/cohort) (126), found a significantly greater reduction in HbA1c at 6 - 12 months after initiating RT-CGM compared to isCGM. (adjusted difference -3 mmol/mol (95% CI -5 to -1); p =0.01), in addition to greater percentage TIR (3.9-10.0 mmol/L) (58.3 ±16.1% versus 54.4 ± 17.1%; p = 0.03) and lower percentage TBR < 3.9 mmol/L (2.2 ± 2.7% versus 6.1 ± 5.0%; p < 0.001) and lower glycaemic variability (34.3 ± 6.1% versus 39.3 ± 7.6%; p < 0.001).

Summary

In summary, isCGM (Freestyle Libre 1) has not been associated with a change in HbA1c compared to SMBG (120-122) but the addition of optional high and low alerts in the later iteration (Freestyle 2) has led to an improvement in glycaemic outcomes (123). RT-CGM has been shown to have a more favourable impact on glycaemic outcomes than isCGM (124-127).

1.3 Insulin bolus dose adjustment

The Landmark Diabetes Control and Complication Trial (DCCT) showed that intensive therapy, defined as using an insulin pump or 3 or more daily injections guided by blood glucose monitoring, delays the onset and slows the progression of the diabetes-related complications of neuropathy, retinopathy and nephropathy (32). However, this is at the expense of an increased risk of severe hypoglycaemia (32). Intensive therapy over a longer period reduces the risk of the macrovascular complications of cardiovascular disease and stroke (128). The more frequently individuals adjust insulin doses for meals rather than using fixed doses, the lower their HbA1c (129).

Insulin dose adjustments can be complex, involving the summation of meal insulin and correction dose insulin (130). Meal insulin is dependent on the quantity of carbohydrate to be consumed (CHO) and the ratio of insulin to carbohydrate for that meal. The insulin to carbohydrate ratio (ICR) is the number of grams of carbohydrate covered by 1 unit of rapid acting insulin. The correction dose is based on the difference between the target and current blood glucose (BG) and insulin sensitivity factor (ISF), which is the reduction in blood glucose

in mmol/L with 1 unit of rapid acting insulin. The insulin bolus dose can be summarised by the following equation (130):

$$\text{Bolus insulin} = \text{meal insulin} + \text{correction insulin}$$

$$= \frac{\text{ICR}}{\text{CHO}} + \frac{\text{current BG- target BG}}{\text{ISF}}$$

Insulin on board refers to active insulin from previous boluses and is subtracted from this equation to avoid insulin stacking (130) in later bolus calculator models.

1.3.1 Factors impacting glycaemic control

There are a range of factors which may impact blood glucose control and therefore require the insulin dose calculated using the formula above to be modified. These include type and quantity of food ingested, the Circadian rhythm, exercise, alcohol, illness, travel, stress, menstrual cycle, pregnancy, work patterns and the weather or temperature (131).

Glycaemic index and glycaemic load

The glycaemic index (GI) can be defined as a "quantitative assessment of a food's carbohydrate content through its effect on postprandial blood glucose concentrations"(132). High GI foods are carbohydrate rich foods which are rapidly broken down during digestion and absorbed into the bloodstream, leading to a rapid increase in blood glucose (133). There are many factors affecting a food's GI value, including types of dietary fibre and the type and structure of the starch (134). A systematic review found that studies suggested the risk of mild hypoglycaemia

was greater with low GI foods compared to high GI foods but the timing of hypoglycaemia was not reported (135). The term "glycaemic load" integrates the GI value with the amount of carbohydrate in a given quantity of food, meal or diet, in order to provide additional information regarding the magnitude of increase and duration of impact on postprandial glycaemia (133). For example, watermelon has a high GI index but low glycaemic load as it contains only a very small amount of carbohydrate (133). A low glycaemic load meal has been demonstrated to induce a gradual postprandial increase in blood glucose levels and sustained nocturnal hyperglycaemia, in comparison to a high glycaemic load meal which peaked earlier at a higher level and returned to basal levels within 5-6 hours (136).

Fat and protein content

The fat and protein content of foods also impacts on postprandial blood glucose levels. The main effect of high fat meals is late postprandial hyperglycaemia and in some studies glucose levels were reduced in the first 2-3 hours, possibly explained by delayed gastric emptying (135). Protein affects blood glucose levels in the late postprandial period and when consumed with carbohydrates, an increase in glucose levels after 3-4 hours has been observed (135).

Exercise

The benefits of exercise for people with T1D include improving fitness, strength and wellbeing and reducing cardiovascular risk factors and insulin requirements (137). Whilst it is recognised that generally aerobic exercise reduces blood glucose levels, anaerobic exercise increases blood glucose levels and mixed aerobic/anaerobic exercise maintains glucose stability, individual responses are dependent on a number of variables including initial blood glucose concentrations, concentration of insulin and counter-regulatory hormones such as glucose,

duration and intensity of the activity, fitness level and nutritional status (138). Strategies aimed at managing blood glucose levels around exercise in order to reduce the risk of hypoglycaemia with aerobic or mixed aerobic/anaerobic exercise include reducing insulin bolus and basal doses and increasing carbohydrate intake (138). It has been suggested that bolus dose reductions prior to exercise are most likely only suitable for exercise with a predictable intensity within 2-3 hours after a meal, with the extent of the reduction dependent on duration and intensity of exercise (138).

International consensus guidance for managing glucose levels during exercise using isCGM/RT-CGM recommends sensor glucose targets stratified by intensity of exercise experience and risk of hypoglycaemia. The inclusion of exercise experience intensity within the guidance (139) is based on a large T1D registry in Germany and Austria suggesting in part that those who do not routinely exercise may be at higher risk of hypoglycaemia (140). This study found that in people aged 18-30 and 30-45 years and in men overall, the highest rate of severe hypoglycaemia was in the inactive group (all $p<0.0001$) and also that severe hypoglycaemia with coma was lowest in the most active group ($p < 0.0001$) (140). High risk of hypoglycaemia is defined within the consensus guidance as those with impaired awareness of hypoglycaemia and/or an episode of severe hypoglycaemia in the last 6 months and/or TBR (<3.9mmol/L; <70mg/d) > 8% (139). The recommended actions to take before, during and after exercise are dependent on the sensor glucose level and trend arrow (139). The CGM alerts, including for glucose rate of change, can be useful to enable earlier mitigating actions, such as carbohydrate consumption or basal rate adjustment (139).

Muscle contraction during exercise leads to an increase in glucose transport independent of insulin and as this effect wears off, it is replaced by an increase in insulin sensitivity facilitated by the translocation of further GLUT4 receptors to the cell surface (141). The increase in insulin sensitivity following moderate exercise may last for up to 48 hours and is accompanied by the rebuilding of muscle glycogen stores (142). People with T1D are at risk of delayed nocturnal hypoglycaemia following exercise in the late afternoon or evening (143, 144). There are conflicting findings for the impact of intermittent high intensity exercise combined with moderate intensity exercise, when compared to continuous moderate intensity exercise alone; Iscoe et al demonstrated a protective effect against nocturnal hypoglycaemia (145) whilst Maran et al found an increased risk of nocturnal hypoglycaemia (146). Post evening exercise, the consumption of a low GI meal with insulin bolus reduction followed by a low GI snack prevented postprandial hyperglycaemia and protected against hypoglycaemia for 8 hours post exercise, however the risk of late postprandial hypoglycaemia remained (144). The addition of a total daily basal dose reduction by 20% for MDI users was found to protect against hypoglycaemia for 24 hours after exercise, when compared to insulin bolus reductions and low GI meal and snack alone (143).

Alcohol

Evening alcohol consumption is associated with lower fasting blood glucose levels the following morning and an increased risk of hypoglycaemia after breakfast (147). Evening alcohol consumption is associated with a reduction in nocturnal growth hormone secretion (147). Whilst this is an association and cannot assumed to be causation, it is acknowledged that growth hormone is a counter-regulatory hormone which increases glucose production by gluconeogenesis and glycogenolysis from the liver and kidney (148).

Illness

It is recognised that blood glucose levels can increase during intercurrent illness even if an individual is not eating and general advice regarding sick day rules includes increasing the frequency of blood glucose monitoring, monitoring blood ketone levels, maintaining fluid and carbohydrate intake and giving additional insulin if blood glucose levels are high and/or ketones are present (149).

Stress

The FinnDiane study showed that individuals with higher perceived stress levels were less likely to consume a healthy diet (150). In normal weight individuals, those with moderate perceived stress had higher mean blood glucose values than those with low perceived stress levels (150). Similarly in lean individuals, those with high perceived stress had higher mean blood glucose concentrations than those with low perceived stress levels (150).

Menstrual cycle

Changes in glycaemic control throughout the menstrual cycle have been observed. Tatulashvilli et al demonstrated that the percentage TIR decreases in a linear manner throughout the menstrual cycle from the early follicular to late luteal phases(151). TAR was significantly higher in the late luteal phase compared to the early follicular phase (151). The TIR was found to suddenly improve at the start of menstrual bleeding (151). However Goldner et al found that glucose patterns related to the menstrual cycle are diverse; whilst some women experience hyperglycaemia during the luteal phase, others have no characteristic pattern to glucose levels throughout the menstrual cycle (152). However this was a very small study (n=4) (152). The

authors highlighted that there is not an established consensus yet regarding the relationship between progesterone or oestrogen levels and insulin sensitivity and there may be other factors impacting glucose metabolism at various points in the menstrual cycle, including cellular, other hormonal and behavioural factors (152).

1.3.2 Carbohydrate Counting

Carbohydrate counting education traditionally taught individuals to work out the number of carbohydrate portions (CP) (1 CP= 10g carbohydrate) (153) in a meal or snack to be eaten but this has largely been replaced by teaching how to calculate the total amount of carbohydrate instead. This can be undertaken by weighing food, looking at food labels or carbohydrate reference lists (154), comparing with food photographs or looking on restaurant websites (153). Individuals can calculate the amount of carbohydrate in their portion by using the following formula (153):

Amount of carbohydrate in their portion (grams) = amount of carbohydrate per 100 grams of the food x (weight of their portion (grams)/100)

Food labels can be confusing, for example it is important to look at the “total carbohydrate” rather than “carbohydrate of which sugars” and to check whether the information refers to the cooked or raw weight of the food such as pasta (153). Smartphone applications are now readily available such as “My Fitness Pal” (155) and “Carbs and Cals” (156) which have nutritional information for a large range of foods accessible from their database.

1.3.3 Challenges of intensive insulin therapy

Whilst there are benefits to insulin dose adjustment as described above, there are a number of barriers to people achieving this, including hypoglycaemia and fear of hypoglycaemia, numeracy literacy, excessive time requirements and data overload (157). Insulin dose adjustment requires numeracy skills to interpret a blood glucose measurement and count carbohydrates accurately, in order to calculate meal and correction insulin doses. People with higher numeracy scores equivalent to at least a C grade at GCSE have a lower HbA1c compared to participants with lower numeracy skills (HbA1c 68 ± 13 mmol/mol compared with 77 ± 18 mmol/mol, $p = 0.004$) (158). Low numeracy skills are common in participants with diabetes (158, 159) as they are in the population as a whole (160). Low diabetes-related numeracy skills are associated with fewer self-management behaviours and an increased likelihood of errors in self-management, for example recognising when a blood glucose value is in range (159).

Carbohydrate counting accurately is challenging and errors can have a detrimental effect on blood glucose control (161). A study found that the mean meal carbohydrate difference between participants' estimation in a real-life setting and the assessment of a dietitian using a computerised analysis programme was high (15.4 ± 7.8g or 20.9 ± 9.7 % of the total carbohydrate content per meal) (161). Larger discrepancies in carbohydrate estimation were associated with increased glycaemic variability and reduced time in range (161).

1.3.4 Structured education

Healthcare professionals can provide training and educational resources for individuals wishing to learn how to count carbohydrates as accurately as possible and interpret blood glucose measurements, in order to make insulin dose adjustments. The intensive approach used in the DCCT trial involved low patient:healthcare professional staffing ratios and frequent outpatient visits/telephone reviews to supervise insulin dose adjustments, which would not be sustainable in most healthcare systems (32, 35). Structured education programmes offer an alternative approach, comprising a fixed curriculum followed by trained educators, in order to teach individuals how to self-manage their T1D more effectively independently (33).

An example of an early structured education programme is the Diabetes Teaching and Treatment Programme (DTTP) initiated in specialist diabetes centres in Dusseldorf/Vienna as a 5 day inpatient group teaching programme (34). This programme taught a novel more flexible self-management approach, in comparison to the more traditional approach taught at the time of a rigid diet, fixed insulin doses and contact with a physician prior to insulin dose adjustment (34). The programme empowered individuals to aim for near-normal blood glucose levels and deal independently with glucose levels out of the target range(34), encouraging the use of twice daily intermediate acting insulin with short acting insulin before meals. Participants learnt how to adjust insulin doses to allow dietary and lifestyle freedom and were encouraged to perform regular self-monitoring of blood or urinary glucose levels to facilitate decision making (34). Follow up at 12 months (n=78) demonstrated an improvement in HbA1c (baseline mean glycosylated haemoglobin above upper limit of normal range 2.6% (±2.0) at baseline versus 1.0% (± 1.7) at one year; $p < 0.001$) (34). There was a reduction in hospital admissions, albeit with different averages given for comparison (baseline mean 10 to median 1 day per participant

per year; $p < 0.001$) (34). A multicentre study demonstrated the feasibility of translation of the DTTP for use in non-specialist general hospitals, with the aim of intensifying insulin therapy safely (162); long term follow up over 6 years (n= 636) found a reduction in mean HbA1c (7.6 ±1.3% during follow up compared to baseline 8.3 ±1.9%; $p < 0.001$) (37). There was a reduction in severe hypoglycaemia for participants with diabetes duration of at least 1 year prior to entry into the study (n= 538) (0.28 during the year preceding the programme versus 0.17 cases/patient/year during the 6 year follow up) (37).

The Dose Adjustment for Normal Eating (DAFNE) study (35) evaluated a 5 day structured education outpatient programme based on the DTTP approach (34), specifically for individuals with moderate or poor glycaemic control (HbA1c 7.5-12.0%) and with diabetes duration of more than 2 years without advanced complications. Participants on the DAFNE course (immediate DAFNE group) (n= 68) had improved glycaemic control at 6 month follow up compared to the control group waiting list (n=72) (mean (SD) HbA1c 8.4 (1.2)% versus 9.4 (1.3)%; $p < 0.0001$) with no difference in severe hypoglycaemia compared to the control group. (35). Participants also reported improvement in the impact of diabetes on dietary freedom, overall quality of life and psychological wellbeing with increased treatment satisfaction (35). The DAFNE course has been widely implemented at centres across the U.K. and observational 1 year follow up has shown an improvement in HbA1c (n= 639) (baseline (mean ± SD) 8.51± 1.41 % versus 1 year post DAFNE 8.24 ±1.29%; difference (95% CI) 0.27% (0.16-0.38); $p < 0.001$) and reduction in the rate of severe hypoglycaemia (n= 501) (pre mean 1.93 (range 0-99) to 0.61 (0-70) episodes/person/year post DAFNE; difference (95%CI) 1.15 (0.73-1.57); $p < 0.001$) (36).

There have also been a number of structured education programmes aimed specifically at improving hypoglycaemia awareness (33). Examples of these programmes are described below (38-40), all running as weekly sessions over a set time period.

The Hypoglycaemia Awareness, Anticipation and Treatment Training (HAATT) Programme (38) is a 7 week psycho-educational treatment programme. The study randomised adults (n=60) with a history of recurrent severe hypoglycaemia in Bulgaria to SMBG (control) or SMBG and HAATT, finding that HAATT was associated with improved detection of low blood glucose events, reduction in frequency of moderate hypoglycaemia episodes (HAATT pre 8.7 to post 5.3 episodes/participant versus SMBG pre 9.7 to post 11.0 episodes/participant; $p < 0.001$) and reduction in severe hypoglycaemia episodes (HAATT pre 2.0 to post 0.4 episodes/participant versus SMBG pre 1.8 episodes to post 1.7 episodes/participant $p = 0.03$), which persisted into long term follow up (38).

The 5 week German HyPOS education programme provided a bio-psychosocial perspective focusing solely on hypoglycaemia, for individuals with severe hypoglycaemia or at risk of severe hypoglycaemia (defined as impaired hypoglycaemia awareness with HbA1c <6.5% and T1D for >10 years) (40). The HyPOS group showed a greater improvement in hypoglycaemia awareness compared to control (standardised education programme) as measured by the hypoglycaemia awareness questionnaire (HAQ) developed by Clarke et al (163) (score difference between treatments 0.7 (95% CI 0.1-1.2%); $p = 0.024$) (40). There was no between group difference in the number of severe hypoglycaemic episodes (follow up difference between groups (95% CI) 0.3 (-0.04 – 1.0) episodes per participant per year; $p = 0.37$) (40).

The DAFNE hypoglycaemia awareness restoration (DAFNE-HART) study was a 12 week single-arm pilot study for individuals (n=23) with ongoing impaired hypoglycaemia awareness (GOLD score ≥ 4) despite completion of the original DAFNE course, using motivational interviewing and cognitive behavioural techniques (39). At 12 month follow up, there was a reduction in the rates of severe hypoglycaemia (median (range) baseline 3 (0-104) versus 0 (0-3) episodes/participant/year at 12 months; $p < 0.0001$) and moderate hypoglycaemia (14 (0-100) baseline versus 1 (0-18) events/participant/6 weeks at 12 months; $p < 0.0001$) (39). This was achieved without a change in HbA1c (baseline 62.0 ± 13.3 mmol/mol versus 61.8 ± 11.7 mmol/mol at 12 months; p= 0.86). Participants demonstrated an improvement in hypoglycaemia awareness as measured by the GOLD score (164) (5.6 ± 1.4 baseline versus 4.5 ± 1.9 at 12 months; $p < 0.029$) and Clarke score (163) (5.4 ±1.2 versus 3.8 ± 1.8; $p < 0.0001$) (39).

In summary, broad structured education programmes providing training in the intensification of insulin therapy and self-management of T1D are associated with an improvement in HbA1c (34-37) and reduction in severe hypoglycaemia (36, 37). Structured education programmes focusing specifically on improving hypoglycaemia awareness have demonstrated a reduction in moderate and severe hypoglycaemic events (38, 39) and improvement in hypoglycaemia awareness (39, 40).

1.3.5 Standard bolus calculators

If individuals are confident carbohydrate counting, they may find an automated standard bolus calculator helpful in order to work out the insulin dose adjustment. Individuals enter a carbohydrate amount. Their blood glucose value is either entered manually or automatically if

the bolus calculator is built into their blood glucose meter. The automated bolus calculator then calculates a suggested insulin dose, using the carbohydrate amount, blood glucose value and pre-set ICR and ISF, as per the formula previously given (130).

It has been suggested that barriers to intensive control can be overcome by technological innovation (157). An automated bolus calculator has been shown to reduce errors in insulin dose calculation from 63% to 6% compared to calculating a dose manually, with increased confidence and a preference for using the meter (165). However, participants were given a carbohydrate value in this study and did not estimate it themselves, therefore eliminating a potential error source. The use of a bolus calculator still relies on people being able to carbohydrate count accurately by looking at food packaging, weighing food and using education resources.

Schmidt el al in their review of bolus calculators (130), describe their evolution from simple sliding scales(166), tables (167) or discs (168) incorporating correction and meal insulin, sometimes including timing recommendations which have become obsolete (166). Intermittent iterations included an electronic pocket calculator with a fixed ISF and graded reduction for exercise, showing a significant reduction in HbA1c (-0.85% intervention versus -0.07% controls, $p < 0.05$) (169).

Garg et al conducted the first study to look at the impact of a Food and Drug Administration approved tool, the Accu-Chek (Roche, Indianapolis, IN) patient decision aid that gives insulin dose suggestions for individuals with T1D on MDI (170) for bolus, basal and correction doses, following the input of a blood glucose value. This used an insulin dosing algorithm based on a

clinician's recommendations loaded into the PDS software and demographic factors. The study demonstrated that the mean HbA1c was lower from 3 to 12 months in the experimental group compared to the control group and that the experimental group maintained the 0.64% reduction in HbA1c (170). However, the experimental group had a significantly higher number of severe hypoglycaemic events compared to the control group (26 vs 8, p = 0.04) (170) which may have been due to not accounting for insulin on board when calculating correction doses (130).

Roche developed the Accu-Chek to incorporate an insulin on board function to try to avoid this potential insulin stacking issue, with the later iteration named the "Accu-Chek Aviva Expert" (Roche Diagnostics, Indianapolis, IN). Individualised ICR and ISFs are inputted and can be varied in time blocks. A number of studies have evaluated this standard bolus calculator as an intervention compared to SMBG and manual dose calculations in participants with suboptimal glycaemic control on multiple daily insulin injections (171-174). The study outcomes can be divided into HbA1c, hypoglycaemia, glycaemic variability and patient reported outcomes.

HbA1c

The ABACUS study (171) was a large multinational randomised control trial of participants with type 1 and type 2 diabetes on MDI with suboptimal glycaemic control (HbA1c >7.5%), showing that those in the intervention group using the Aviva Expert meter, achieved a greater HbA1c reduction from baseline than those in the control group (mean (SD) -0.7% (0.7) vs -0.5% (0.7), one sided p <0.05). This is in contrast to the EXPERT study (174) and CMBDI study (173), in which there were significant decreases in HbA1c in both the intervention phase/arm using the Accu-Chek Aviva Expert and the control phase/arm but no between group

significant difference in HbA1c change. In the BOLUSCALC study (172), there was a significant change in HbA1c in both the carbohydrate counting arm (mean -0.8% (95% CI -1.3 to -0.3%); p = 0.002) and the carbohydrate counting/bolus calculator arm (-0.7% (-1.0 to-0.4%); p < 0.0001) with no significant between group difference (0.1% (95% CI -0.6 to 0.4); p = 0.756). There was no significant change in HbA1c in the third arm which was the control group (-0.1 (-1.0 to 0.7)%; CI only, p value not stated) (172). This finding of no change in HbA1c in the control group of the BOLUSCALC (172) study was in contrast to the HbA1c reduction seen in the control groups of the EXPERT (174) and CMBDI (173) studies. This difference in HbA1c change in the control group may be explained by the control group in the BOLUSCALC (172) study not receiving any education around carbohydrate counting and flexible intensive insulin therapy, whereas this education was provided to the control group in the EXPERT (174) and CMBDI studies (173).

The ABACUS study (171) demonstrated that a significantly higher proportion of participants in the intervention arm using the Expert meter achieved a HbA1c decrease of > 0.5% compared to the control arm (56.0% versus 34.4%; p 0.01). Conversely, the CBMDI study (173) showed no significant between group differences in the proportion achieving a HbA1c reduction of 0.5% ; however the baseline HbA1c in this study was lower than that in ABACUS (171)(8.4% vs 8.9 %) which the authors postulate may have had an effect (173).

Hypoglycaemia

Data has showed no differences between bolus calculator and control groups in terms of frequency of severe hypoglycaemia (171, 173). In the ABACUS study (171) significantly more participants in the intervention group reported hypoglycaemia <70 mg/dl compared to

the control group (n=43 vs n=31, $p < 0.05$), unrelated to a HbA1c reduction of > 0.5 mmol/mol. The CMBDI study (173) showed a reduction in hypoglycaemic events (<3.9 mmol/L; <70mg/dL) in the bolus calculator group over a 2 week period at baseline compared to at 4 months (mean 8.4 (95% CI 6.6-9.8) versus 6.5 (5.2-7.8); $p = 0.022$) that was not demonstrated in the control group (6.7 (4.9-8.5) versus 5.9 (4.3 -7.4); p value not provided). Even though the baseline number of hypoglycaemic events per 2 week period in the bolus calculator group appears that it may be higher than in the control group, the difference was not found to be statistically significant ($p = 0.15$). The reduction in hypoglycaemic events in the intervention group may be explained by the insulin on board calculator and use of more individualised ISFs, which became less aggressive in this group. However, the between group differences in the overall number of hypoglycaemic events was not significant and this is in line with other studies (172, 174). The extension phase of the CMBDI study (175) showed a reduction in postprandial hypoglycaemia with use of a bolus calculator for 4 months, in line with the EXPERT study (174).

A survey of respondents with 4-12 weeks of prior bolus calculator use (n = 588) (176), found 52% indicated reduced fear of hypoglycaemia. In randomised controlled trials, the evidence is equivocal. The BOLUSCALC study showed no significant difference in change in fear of hypoglycaemia score between intervention and control groups over 4 months (172). The CMBDI study showed use of a bolus calculator does not change participants fear of hypoglycaemia after 4 months (173) but does reduce fear if used for 8 months (Fear of Hypoglycaemia (FH-15) questionnaire score (177) mean (SD) 28.24 ± 8.18 basal versus 25.66 ± 8.02 at 8 months; $p= 0.026$) (175), suggesting perhaps increased confidence in the device over a longer period.

Glycaemic variability

The EXPERT study (174) and CMBDI study (173) showed no change in glycaemic variability ,including mean amplitude of glycaemic excursions (MAGE), during the control/intervention arms or phases and no differences between groups/phases. However, these results should be interpreted with caution given that both studies (173, 174) used SMBG values to calculate markers of glycaemic variability, except for MAGE in the EXPERT study (174), which was calculated from blinded CGM for the first and last week of each phase. SMBG provides only a snapshot of glucose values over a 24 hour period. These values may be biased towards hypo and hyperglycaemia, if participants are symptomatic and test more at these times. Conversely, the ABACUS study showed the use of a bolus calculator was associated with a reduction in MAGE (mean (SD) MAGE bolus calculator -20.2 mg/dL (41.4); $p < 0.01$ versus control 2.9 mg/dL (32.1); p value stated as not significant), even if the HbA1c improvement was less than 0.5% (171). This improvement in MAGE was only observed in older participants (171). Whilst blinded CGM was used to calculate the MAGE in this study, it was only worn by a subset of participants and therefore these results may not be applicable to the whole study population.

Patient reported outcomes

Use of an standard bolus calculator is associated with a greater treatment satisfaction scores (174) or a greater improvement in these scores than in the control arm (171), although in the EXPERT study these scores were derived from an unvalidated ad hoc questionnaire (174). Results from the CMBDI study suggested that a longer duration of use of 8 months was associated with increased treatment satisfaction, not observed after 4 months of use (173, 175). The EXPERT study (174) found that use of a bolus calculator was associated with an improvement in Diabetes Quality of Life Related to Diabetes questionnaire scores (Spanish

version) (Es DQOL) (mean (SD) intervention baseline 92.88 (20.96) versus final 89.39 (20.83); $p < 0.05$) with lower scores indicating higher quality of life. However, there were no between group differences in scores compared to the control group.

Lawton et al interviewed people with T1D (n=42) who had attended a structured education course which included training in the use of bolus advisors (178). Reasons for using a bolus calculator and the perceived benefits were broadly categorised into a gratitude and reliance on a bolus calculator in those with self-reported poor mathematical skills, to save time and effort and for the data storage facility (178) .

Summary

In summary, a standard bolus calculator has been shown to lead to a reduction in HbA1c compared to control at the expense of increased hypoglycaemia (171), or is associated with no significant difference in HbA1c change or hypoglycaemia frequency compared to control (173, 174). Markers of glycaemic variability should be interpreted with caution as they are mostly calculated from SMBG (173, 174) or only a subset of participants wearing blinded CGM (171). Use of a standard bolus calculator is associated with an improvement in treatment satisfaction (171, 174, 175).

Whilst it has been shown that the use of a standard bolus calculators may be beneficial, the insulin to carbohydrate ratio and insulin sensitivity factor are fixed and do not automatically adjust in response to lifestyle changes, such as reduced exercise or changes in weight. Most individuals wait until review by a healthcare professional before making any changes to bolus

calculator settings, with reasons cited including lack of confidence, self-perceived poor analytical skills, not knowing how to change the settings or believing that their ratios and targets never need to be changed (178). A high proportion of individuals using CGM download data infrequently (118) and some prefer to review retrospective downloads with their healthcare professional (115). It has been suggested that blood glucose monitoring and CGM can lead to data overload when a clinician has limited time with a patient, in order to interpret the data and suggest treatment changes (157). If this data could be analysed by an intelligence support system able to suggest therapeutic changes, this could enhance the value of a blood glucose meter and bolus calculator (157).

1.4 Early Decision Support Systems

Early Decision support systems (DSS) used clinical algorithms, employed knowledge based systems or used model based simulations of glycaemic profiles to test possible new therapeutic regimes, which could be done in an automated optimisation mode (179). An early dual units was also developed to enable a medical unit to receive data from a patient unit and send a new treatment protocol back to the patient unit (180). Early DSSs utilising these techniques are described in further detail below with examples of each.

1.4.1 Clinical algorithms

DSSs can use clinical algorithms based on routine clinical experience, such as the DIABETES expert system (181), which used input values of the insulin regime type, blood glucose values and symptoms of hypo/hyperglycaemia in a production rule system using static and dynamic knowledge, for example “IF patient is on regime A, THEN their pre-lunch blood glucose should not be low AND they should not have symptoms of hypoglycaemia before lunch”. This

generated an assessment of glycaemic control and explanation of recommended adjustments to their insulin regime. Testing the system on 600 patient cases compared to a "medical expert", found full agreement in 47% of cases (181), however sometimes the system suggested a solution which was different to the specialists but not incorrect.

Neural nets offer an alternative approach to decision making using patient factors usually taken into account by clinicians, such as age and activity, as input nodes (182). The output nodes are the insulin regime (182). Specific advantages to neural nets include the ability to retain data and a fast recall time; the main disadvantage being the time required for training, although this was found to decrease with increasing input nodes such as adding fever or surgery (182).

1.4.2 Knowledge based systems

Limitations to clinical algorithm based systems described above include the need for a very large rule set to deal with every possibility and challenges coping with complex situations or where perhaps more than one rule applies (179). These challenges led to the development of knowledge based systems, which apply broad medical knowledge to new situations (179). An example of a knowledge based system is the Automated Insulin Dose Advisor (AIDA) (183), which allowed more flexibility in splitting the day into 13 periods, employing a reasoning approach to generate a problem list and then control actions to help solve the problems. The control actions were filtered, in case one action could worsen a second problem and then ordered (183). The integrated system then allowed the simulation of qualitative advice from the therapeutic advisor using the clinical model, for example in the form of a graph to represent predicted glucose over time, in order to select an optimal solution (183).

1.4.3 Model based simulation/optimisation systems

Model based simulations predict the effect of suggested recommendations, in order to guide therapeutic decisions. Models can be run in simulation mode, where the clinician manually experiments with different therapeutic plans to choose what is the best regime in their opinion (179). An example of a model running in simulation mode is the integrated AIDA system as described above (183). Alternatively models can be run in optimisation mode, where the best therapeutic decision is selected automatically (179). Examples of models running in optimisation mode which are described below are the Karlsberg Diabetes System (184) and Diabetes Advisory System (185).

The Karlsberg Diabetes Management System (KADIS) (184) integrated CGM and data entered by participants and then analysed this data to detect areas of concern (184). It then used in silico models to determine the insulin doses and carbohydrates required to optimise the blood glucose curve and presented these results in a report to the physician (184). An outpatient study randomised participants to CGM only or CGM in combination with KADIS advice (184). The use of KADIS with CGM in people with diabetes (53.1% type 1, 46.9% type 2) led to a reduction in HbA1c compared to CGM alone (mean change in HbA1c -0.34% (95% CI -0.56 to -0.12) versus 0.27% (-0.02 to 0.55); $p < 0.01$) with a reduction in mean sensor glucose (8.43 ±1.33 mmol/L at baseline to 7.59 ± 1.47 mmol/L, $p < 0.05$) and a reduction in hyperglycaemia without increasing hypoglycaemia (184). The diabetes type was not found to have an effect on change in HbA1c (184). A large observational study using KADIS with people with diabetes and cardiovascular disease, demonstrated a decrease in HbA1c if baseline HbA1c was > 6.5% (186). However this result cannot be extrapolated to individuals with T1D, given than the majority had type 2 diabetes (186).

The Diabetes Advisory System (DIAS) (185) used a causal probability network model of glucose metabolism, taking into account the uncertainty of blood glucose prediction when aiming to optimise therapeutic regime (179). Rather than predict a specific blood glucose value, the model gave a probability distribution for the blood glucose at 1 hour intervals over a 24 hour period, dependent on mapping the probability of various physiological parameters in the model (185). These parameters included those that increased blood glucose level (carbohydrate absorption and glucose production) and those that decreased blood glucose level (renal loss of glucose, insulin-independent glucose utilisation, insulin dependent glucose utilisation) (185). In predictive mode, a small study (187) showed the DIAS was able to predict nocturnal hypoglycaemia in 6 out of 8 participants which had not been detected by or been suspected by a doctor, which was confirmed by SMBG in 5 participants. The model could also be run in optimisation mode, by applying a penalty grading system for hypoglycaemia and hyperglycaemia (185). The model then ran simulations to calculate the impact of a change in insulin regime to blood glucose penalty scores and selected the therapeutic regime with the lowest penalty score (185). However, this application has been limited by the high mean prediction error of 3.3 mmol/L (185).

1.4.4 An Early Dual unit system

Early work by Bellazzi et al (180, 188) described a medical unit in the physician's office which periodically analysed data of blood glucose and urine glucose dipsticks transmitted from the patient unit, to assist the clinician in suggesting a treatment protocol. The treatment protocol included insulin regime, diet and exercise which was sent to the patient unit (180). The medical unit performed a three steps process; data interpretation, logic based algorithmic reasoning and a decision step to adjust or choose a new treatment protocol (180).

1.4.5 Benefits and limitations of early Decision Support Systems

Early DSSs offered some potential benefits. They could suggest frequent adjustments to insulin doses, which people only usually receive at clinic and may not have felt confident to do themselves between visits. Patient units with simple algorithms could detect dangerous events such as hypoglycaemia requiring urgent action and immediately alert the patient to this (188).

Limitations of the older DSSs include inadequate data entry, inflexible therapeutic recommendations or recommendations based on historical insulin regimes, unreliable transmission of data and accountability. There were also challenges in selecting an appropriate method to evaluate the system and in the ability of the DSS in dealing with complex problems and a heterogenous patient population. These limitations are described in further detail below.

Some DSSs had limited data entry with no information regarding exercise or nutrition, for example the rule-based DIABETES expert system (181). If systems did include nutritional information, they may have suggested changes such as reducing carbohydrate intake (184) to try to improve blood glucose control. Newer systems adopt a more flexible insulin adjustment approach (189), rather than asking a person to change their dietary intake or exercise routine. Older systems were often modelled on mixed or intermediate insulin rarely used now (180, 184, 185).

Another problem has been unreliable transmission of data, essential for an exchange of information, particularly when a clinician must approve all the recommendations to send back to the patient unit (180). Use of a DSS raises questions around transparency and accountability.

It is important that individuals are able to view an explanation of reasoning in the handheld devices (190), which can then be challenged by patients and clinicians and may improve patient compliance with the suggested actions. The issues of safety and who is accountable medico-legally for the recommendations suggested (190) may also deter patients or physicians from their use.

The selection of an appropriate method to evaluate a DSS can be challenging. Some DSSs have been evaluated by comparing recommendations to those given by a "medical expert"(181). However experts demonstrate diversity in solutions when presented with the same problem (191) and may disagree with a recommendation suggested by a decision support system when it is not incorrect, just a different way of solving a problem (181). Using the DELPHI method can help experts come to a consensus opinion (191) but often in practice limited resources leads to often only one clinician reviewing data.

Whilst decision support tools can help save time in a busy clinic setting, it has been suggested that perhaps they would be best reserved for the more "routine problems", allowing specialist clinicians to spend more time with complex patients with suboptimal glucose control (190), particularly if there are concerns over the ability of decision support tools to process and deal with complex problems. It could be argued that a clinician's expertise may be required to determine glucose targets on an individualised basis, for example the acceptance of higher blood glucoses to avoid hypoglycaemia is preferable in an older person living alone, compared to a newly diagnosed teenager and this may not be taken into account by the models running in automated optimisation mode (179).

1.5 Development of Decision Support Systems

Decision support systems have developed over time in order to overcome some of the limitations of the earlier systems as described in the previous section. Some newer models employ a refined model based simulation/optimisation algorithm, whilst others have used the principles of run to run control and case-based reasoning (Table 3). These systems are described in further detail below.

1.5.1 Model based simulation/optimisation

Examples of more recent DSS employing model based simulation/optimisation are the systems developed by Breton et al at the University of Virginia (192) and the algorithm evaluated by Bell et al (193).

The DSS developed by Breton et al at the University of Virginia requires at least 14 days of data to power it (192). It identifies hypo and hyperglycaemia risk and re-simulates the day with different insulin profiles, in order to determine which will reduce the risk and then suggests changes to the insulin regime accordingly (192). Changes are suggested to the ICRs, ISFs and either basal rate patterns (CSII) or total basal dose and timings (MDI) (192). The DSS also includes a real-time CGM-informed bolus advisor, which adjusts insulin boluses based on current insulin sensitivity and an exercise advisor, which provides behavioural advice to reduce the risk of hypoglycaemia during or shortly after an exercise period (192). The behavioural advice recommends carbohydrate ingestion and/or basal rate suspension, dependent on level of hypoglycaemia risk. A randomised cross-over study (n = 24 adults and adolescents) (192) comprised experimental and control (standard home insulin therapy) admission periods, each

over 48 hours and separated by 4 weeks. These admission periods included varied standardised meals and two exercise episodes. A summary of suggested changes to the insulin regime generated by the DSS, based on the preceding 4 weeks of data, was provided to the physician for approval prior to the experimental admission (192). Use of the DSS was associated with a reduction in daytime glycaemic variability (co-efficient of variation 0.36 ± 0.08 vs 0.33 ±0.06, p = 0.045) and reduction in percentage TBR <70mg/dL (3.2% (1.3% to 4.8%) versus 0.9% (0.4% - 2.3%); p = 0.018) compared to control (192).

Bell et al (193) evaluated an adaptive model-predictive bolus (MPB) algorithm, combining an insulin pharmacokinetic/pharmacodynamic model with an insulin sensitivity model and meal absorption model. This was used to generate an optimal insulin dose, split and duration to minimise the MPB glucose area below target from 0-120 minutes after and above target from 120 to 360 minutes after the meal, saturated by safety constraints (193). CSII users (n=10) consumed high fat, high protein (HFHP) and low fat, low protein (LFLP) meals in random order with an identical insulin bolus calculated using their ICR and delivered as a combination bolus, with 50% up front and 50% delivered over 2 hours (193). On future visits, the dose for the HFHP was calculated using the MPB algorithm and visits were repeated until set glucose targets were met (193). The MPB algorithm for the HFHP meal compared to the combination bolus delivered as 50%/50% over 2 hours decreased the incremental area under the curve (11,712 ± 3172 mg/dL min versus 27,092 ± 1709 mg/dL min; p = 0.0013) and the incremental change in blood glucose concentration (24 ± 11 mg/dL versus 73 ± 4 mg/dL; p =0.001) (193).

1.5.2 Run to Run control

Principle

The principle of run to run control is that each day is considered as a run and the ICR for each meal within the day is adjusted independently on the basis of a performance measure, in view of the postprandial glucose response for the same meal on a previous day (194). This process is repeated until the algorithm converges on a set target with a defined period or number of runs (195). Palerm et al (194) tested the validity of their in silico model for 11 participants on pump therapy with mixed meals rather than oral glucose loads.

The original performance measure in the algorithm took into account the rate of change of postprandial glucose over 60 minutes and meal carbohydrate content; however the new proposed ICRs did not correlate well with ICRs proposed by clinicians using set criteria based on real patient data (194). The performance measure was therefore modified to take into account the estimated postprandial glucose at 60 minutes and the differential between the final and baseline glucose measurements (194). The algorithm using this revised performance measure showed a high correlation with the clinicians' decisions ($r = 0.95$) (194).

Studies using the run-to-run control algorithm

The run-to-run algorithm developed by this group was tested in a 10 week study for participants on CSII ($n = 14$) (195). The purpose of the initial phases was to derive information for the settings and to fine tune the algorithm. In the final phases, the algorithm suggested changes to the pre-prandial insulin dose, in terms of amount and timing, which could be implemented the following day if approved by a physician (195). The algorithm adjusted the insulin dose for

lunch only for one week and then for all three meals for the final one week. This study highlighted the important limitation that participants need to use the run-to-run algorithm for long enough in order for it to converge. In the three meal phase, only 41% of subject-meal responses were convergent in 3-4 days, with 26% always in range anyway and 33% divergent or using incorrect sensitivities or other mitigating circumstances. Participants in this study demonstrated an improvement in HbA1c from baseline of 6.5 ± 0.7% to an end HbA1c at 10 weeks of 5.6% ± 0.2% ($p<0.003$) (195), despite intentional changes to the timing and doses of insulin to aim for postprandial hyperglycaemia during part of the study. This improvement in HbA1c cannot solely be attributed to the run-to-run control algorithm, which only adjusted doses for the last 2 weeks. Potential contributory factors included an individualised set dietary plan, excluding routine snacks and daily contact with a clinician using an intensive insulin regime, which is unrealistic in a real world setting (195).

The run-to-run algorithm as previously described (194) was refined to allow for variable carbohydrate content in three meals per day and tested in another study by the same group (n=9) (196). In this study, the run-to-run algorithm was used for longer for breakfast and dinner than in the previous study (195); this time over a two week period for all three meals (196). Participants were contacted daily to provide data for the previous 24 hour period; the algorithm would then recommend a updated ICR for each meal for the following 24 hours, which would require physician approval prior to implementation (196). This study found the 1 hour postprandial glucose levels before and after convergence were different for each meal ($p = 0.013$ breakfast, $p = 0.023$ lunch, $p = 0.0018$ dinner). The algorithm led to an improvement in postprandial glucose levels; 2 hour postprandial blood glucose values (96.5 ±18 mg/dL) approached pre-prandial levels (90.1 ± 13mg/dL) and postprandial hypoglycaemia frequency was thought to be in line with observations in clinical practice.

There are a number of limitations to the studies above which employed the run-to-run algorithm (195, 196). The algorithms have not been tested with out of range pre-prandial glucose values. They included insulin bolus underdosing to induce postprandial hyperglycaemia in order to allow the algorithm to then converge to within target postprandial glucose levels (194, 195). Despite a reduction in insulin bolus dose, some participants remained in the "deadzone" whereby their postprandial glucoses stayed in the target range, thereby not permitting the algorithm an opportunity to work (195). The first study involved a professional chef preparing the meals with fixed calorie and macronutrient composition in collaboration with a dietician (195), which is unrealistic in a real world setting. It can be challenging for people to follow a strict diet; five participants from the fourteen recruited withdrew, three of these were due to poor compliance with dietary and glucose monitoring (195). Additionally, it is recognised that the fat and protein content influence postprandial blood glucose levels (135). It may be more challenging in real life for the algorithm to converge if the fat, protein and carbohydrate composition of meals are varied. In the follow up study, the participants were usually on low carbohydrate diets (196), therefore the algorithms may take longer to converge if higher carbohydrate meals are consumed.

All participants were on CSII with optimised basal rates and the algorithm only adjusted insulin boluses (194-196). However there have been promising results in simulation using run-to-run control to adjust the basal rates (197), taking on average less than a week to converge. Run-to-run techniques have since been used to adjust both bolus and basal doses in a small pilot study for MDI users (198). A randomised parallel study of children and adolescents (n =21) at a summer camp with isCGM compared daily adjustments made by the DSS algorithm over 11 days to those made by physicians (198). The DSS algorithm estimated the therapy parameters which would have resulted in optimal control in a specific day and incorporated these with

values estimated from previous days using the run-to-run update rule. The DSS algorithm adjusted ICRs and basal doses based on the previous day's data, requiring physician approval prior to implementation (198). The acceptance rate was high; 92% of algorithm adjustments were accepted by the physicians. The time in range and number of hypoglycaemic events were comparable between groups (198).

1.5.3 Case-based reasoning

Principle

Case-based reasoning (CBR) (199, 200) involves retrieving the most similar previous case when presented with a new problem, such as breakfast after exercise, reusing a previously adapted solution as the ICR and then reviewing the postprandial glucose level as the outcome. The system learns from this case by revising it and storing it in the case base (Figure 2).

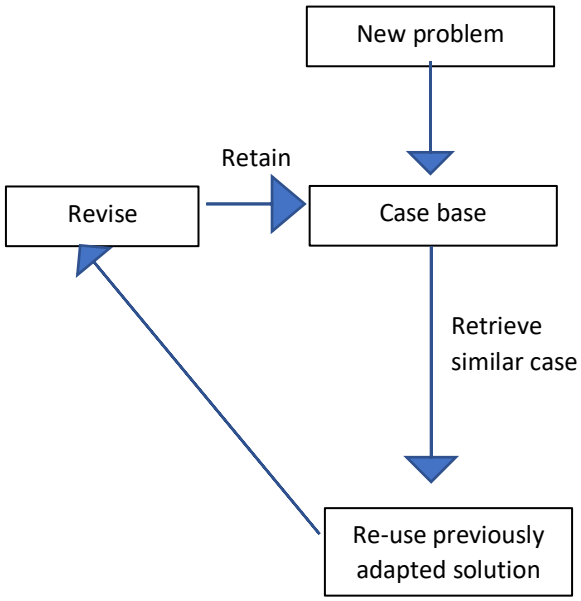


Figure 1.1: An overview of the case-based reasoning principle, as described by Aamodt et al (199)

Studies using Case-Based Reasoning

There have been a number of DSSs employing case-based reasoning. Examples of DSSs employing case-based reasoning are the 4 Diabetes Support System, the Advanced Bolus Calculator for T1D, Daily Dose and the Patient Empowerment through Predictive Personalised Decision Support (PEPPER) system (201), which are described in detail below.

a) 4 Diabetes Support System

The case base can be built up from individual patients. For example Schwartz et al identified 50 cases of patient problems, solutions and outcomes (202) during a 6 week preliminary study of 20 participants on CSII, which they grouped into 12 distinct problem types. This case base facilitated prototypical software development to recognise these problems automatically from large volumes of clinical data and glucose readings and then offer decision support to physicians based on learned experience (202). Evaluation of this DSS, called the "4 Diabetes support system" (203), in a follow up study found that 97.2% of these problem detections were correctly identified by the system as verified by clinicians and 96.1% were deemed to be useful. A matching case with a beneficial solution was retrieved 82% of the time (203). The detection rate was higher for those wearing CGM. It is noteworthy that the system detected only 2.6 problems/participant/week in this study (203) compared to 4.9 problems/participant/week in the preliminary study (202) ($p = 0.017$), which may be attributed to CGM data from only 6 out of 23 participants and the omission of life event data reporting in the follow up study, such as illness and exercise. This was felt to be too time consuming for participants in the preliminary study and a contributing factor to the high drop out rate of 40% (202).

b) Pilot Clinical Assessment of a Novel Advanced Bolus Calculator for T1D Study

The pilot Clinical Assessment of a Novel Advanced Bolus Calculator for T1D (ABC4D) study (204) was a 6 week non-randomised single arm study using CBR (n = 10) for participants on MDI. This study demonstrated safety of the system and acceptability. The smartphone platform displayed an insulin dose recommendation to participants, following their input of carbohydrate intake, capillary blood glucose, exercise, alcohol and meal absorption speed. Participants attended the research facility on a weekly basis to upload the ABC4D data from their smartphone and the blinded CGM data onto the clinical revision platform. The study team reviewed the proposed adaptations to ICR for each case such as breakfast, prior to updating the ICRs and sending the revised adapted case solution to the participants' smartphones. There was a trend towards a reduction in post-prandial episodes of hypoglycaemia within 6 hours (median (IQR) 4.5 (2.0-8.2) in week 1 versus 2.0 (0.5-6.5) in week 6 (p = 0.1)), with no episodes of severe hypoglycaemia (204). There was a trend towards reduction in percentage of time in hypoglycaemia at all thresholds and increase in percentage time in range without an increase in time in hyperglycaemia (204); the differences did not reach statistical significance in view of the small sample size.

The case parameters used in this pilot study can be categorised by automatic or manual input: automatic input parameters were meal time (breakfast, lunch, dinner) and pre-prandial hyperglycaemia (>270mg/dL) and manually input parameters were exercise, alcohol, and meal absorption rate (200). The most frequent manually entered parameter was exercise (mean (± SD) 8.4% ± 6.3% of all retrieved cases), then alcohol (5.5% ± 6.0%). Absorption rate was entered the least frequently (1.8% ± 2.1%) (200). Participants completed a questionnaire at the end of the study to provide feedback regarding the case parameters; 80% thought it would be

useful to add extra information about the case parameters alcohol and exercise (200). There were suggestions that inputting the type and duration of exercise, in addition to intensity, could be useful (200). Whilst additional parameters may take into account some of the many factors affecting glucose levels, it would firstly lead to an increase in the number of cases and therefore potentially result in a longer convergence time and secondly require more input by the participant, possibly impacting usability (200), which was evident in the preliminary study by Schwartz et al described above (202).

c) DailyDose DSS

The DailyDose DSS is an iPhone application providing real-time insulin bolus advice and up to five weekly recommendations for insulin dose adjustments, including to the basal dose, ICR or ISF at particular times of day, using a case-based reasoning algorithm (205). Participants could accept or reject each recommendation; if accepted, the change would then be implemented in the application settings. DailyDose also provided advice to manage blood glucose around exercise, recommending a reduction in bolus doses or additional carbohydrate intake (205). The single arm proof-of-concept study in adult MDI users (n=25) demonstrated no significant difference in TIR or other glycaemic outcomes during the 8 week period of using DailyDose compared to the baseline 2 week period of using CGM only (205). The results suggested that trusting the DailyDose system was associated with an improvement in percentage TIR; in a post-hoc analysis, weeks when more than 50% of recommendations were accepted and followed within a week were associated with an improvement in TIR of 6.3%, compared to weeks when 50% or less of recommendations were accepted and followed within a week (95% CI 2.5-10.1%; $p = 0.001$) (205). Limitations include the small size and lack of control arm.

d) The Patient Empowerment through Predictive Personalised Decision Support (PEPPER)

The Patient Empowerment through Predictive Personalised Decision Support (PEPPER) system included a real-time adaptive insulin bolus advisor employing a case-based reasoning algorithm and a safety system (201). The safety system provided predictive low glucose alerts, predictive low glucose suspend for pump users, personalised carbohydrate recommendations to correct hypoglycaemia whilst minimising hyperglycaemia and a dynamic insulin bolus constraint to saturate changes to the ISF/ICR (201). Case revisions proposed by PEPPER were reviewed by a clinician twice weekly and if accepted, these were stored in the case base for future use (201). A randomised controlled crossover study compared PEPPER (intervention) to standard bolus calculator (control) in MDI and pump users (n =54) (201). The duration of each treatment arm was 12 weeks with a 3-4 week washout period (201). There were no differences in glycaemic outcomes or measures of glycaemic variability observed between the intervention and control (201). A sub-analysis of the MDI cohort (n=25) showed no differences in glycaemic outcomes or glucose variability between intervention and control (201).

1.5.4 Other Decision Support Systems

Studies evaluating decision support systems in MDI users

Several studies have evaluated DSS specifically for MDI users (206, 207), in addition to the ABC4D pilot study (204), DailyDose study (205) and study by El Fathi et al (198) as described previously. These studies are described in detail below (Table 3).

The inControl Advice DSS (TypeZero Technologies, Charlottesville, VA, USA) integrated CGM and smart connected insulin pens and had the following features: bedtime advice, prediction of hypoglycaemia risk with mitigating treatment advice including at bedtime and at the onset of exercise and a twice weekly MDI treatment optimisation routine (207). A 14 week randomised parallel study in adults and adolescents comparing the inControl Advice DSS with CGM (n =57) to CGM only (n = 23) (2:1 allocation) found no significant differences in glycaemic or patient reported outcomes between the groups (207). Per-protocol analysis assigned inControl Advice users a score, based on average daily number of interactions with key app functions, in order to categorise users into active (n = 18) or non-active (n = 39) users (207). Active use of the system was associated with a reduction in hypoglycaemia risk; active users had a greater reduction in percentage TBR at various thresholds (<70mg/dL; <60mg/dL; <54mg/dL; <50mg/dL) and greater reduction in low blood glucose index (LBGI) compared to non-active users (-0.9 versus 0; p = 0.008) (207). However, baseline TBR values at all thresholds appear higher for the active group compared to the non-active group but the differences were only reported for percentage TBR <70mg/dL (active users 5.5 (1.1-8.8) vs non-active user 3 (1.2-5.3); p = 0.134).

A retrospective quality improvement project with a before and after design evaluated the intervention of the Glytec Glucommander Clinical Decision Support System (CDSS) (Glytec, Greenville, SC, USA) with an integrated bluetooth and cellular-enabled blood glucose meter (206). The CDSS recommended insulin basal and or bolus dose adjustments to a nurse, who communicated changes to patients between clinic visits. The nurse ran the CDSS software at 3,7,14 or 28 day intervals to generate insulin dose adjustments; interval length was determined by the CDSS dependent on glycaemic control (206). There was a reduction in HbA1c over a 12 month period (7.2% at 12 months versus 10.2% at baseline; p < 0.00001) (206). Patients

were referred into the clinic from their HCPs with the aim to improve glycaemic control (206), which could explain the high baseline HbA1c. Limitations include retrospective study design with lack of a control group and therefore it is impossible to determine the impact of regular contact with the nurse between clinic visits on HbA1c. Additionally the majority of participants had type 2 diabetes (T1D n = 11 (24%); type 2 diabetes n=35 (74%)), therefore limiting extrapolation of results to the T1D population (206).

Studies evaluating decision support systems in combined pump and MDI populations

Whilst the studies above have evaluated DSSs exclusively in MDI users, there have been a number of studies evaluating DSS in combined pump and MDI user populations. The DSS developed by Breton et al using model based simulation/optimisation (192) and the PEPPER system using a CBR algorithm have been described previously (201). A further example is the Tele1Diab study (208), which is described below.

The Tele1Diab study evaluated the Diabeo system, which included automatic algorithms for the adjustment of ICR and basal insulin dose or rate when postprandial or fasting glucose levels were out of target (208). The change in HbA1c from baseline to 6 months was different between the control group (usual quarterly visits) and Diabeo with quarterly visits (mean (SD) +0.2 (± 0.8) versus -0.5 (± 0.9); $p \leq 0.001$) and between control and Diabeo with teleconsultation every 2 weeks (+0.2 (± 0.8) versus -0.7 (± 0.8); $p \leq 0.001$) (208). Whilst there was no difference between the three groups in terms of total time spent on follow up (telephone/face to face), the control group and Diabeo with quarterly visits group spent an additional 274 ± 178 minutes or 288 ± 218 minutes respectively travelling to and from the hospital, completing administration tasks and waiting (208). This highlights the time saving potential of a DSS with a smartphone

application uploading data to a website or portal which can then be viewed by a clinician to facilitate teleconsultations.

Studies evaluating decision support systems in pump users

There have been several decision support systems evaluated exclusively in pump users, including by Zisser et al employing run-to-run control as described previously (195, 196), by Nimri et al (209), the Pumptune system (189), the insulin sensitivity-informed bolus calculator employed in the Diabetes Assistant (DiAs) (210) and a novel adaptive artificial pancreas system (211) (Table 3). These studies are discussed in detail below.

The DSS Pumptune (189) is a modified proportionate-integral-derivative (PID) controller algorithm which uses a scoring system to model glucose concerns based on the glucose value and glucose rate of change within the next hour. In this model, "glucose concern" scores are positive if there are concerns regarding hyperglycaemia and negative if there are concerns regarding hypoglycaemia (189). However the scores are not linear, as a decreasing blood glucose if already hypoglycaemic is more concerning than a higher blood glucose which is decreasing. Therefore if already hypoglycaemic, Pumptune will generate a more negative "glucose concern" score (189). Pumptune recommends changes to basal rates, ICRs and ISFs in proportion to their predicted contribution to the insulin activity over each hour (189). In a randomised crossover study in children on CSII (n = 22) with settings adjusted by a physician or Pumptune, Pumptune was associated with increased time in target (63.4% vs 57.4%, p = 0.016) with no effect on hypoglycaemia (189). However, this study is limited by the short duration of each study period (6.5 days) and the fact that settings were only adjusted once prior to each study period.

Nimri et al have evaluated the Advisor Pro (DreamMed Diabetes Ltd, Petah Tikva, Israel) in a parallel RCT in children, adolescents and young adults (n=108) over a 6 month period (209). The Advisor Pro analyses 3 weeks of data to recommend adjustments to the basal rate, ICR or ISF and also provide personalised behaviour recommendations regarding the way insulin is delivered, such as missed boluses or timing of bolus injections (209). Participants were randomised to receive remote insulin dose adjustment advice every 3 weeks from the Advisor Pro or a physician. Percentage TIR (3.9-10mmol/L (70-180 mg/dL) and percentage TBR (<3.0 mmol/L)(<54mg/dL)) within the Advisor Pro arm were statistically non-inferior to the physician arm (TIR 50.2 ± 11.1% versus 51.6 ± 11.3% respectively; p <1 x 10^7) (TBR 1.3 ± 1.4% versus 1.0 ± 0.9%; p <0.0001) (209). There was no difference in HbA1c change between the two arms (209).

Fabris et al evaluated an insulin sensitivity (IS)-informed bolus calculator (210) employed in the Diabetes Assistant (DiAs), which used the ratio of usual IS derived from the data collection period with an estimate of real-time IS at the time of the bolus. The algorithm used CGM and pump data with a glucose-insulin dynamics model to estimate the IS index (210). The IS-informed bolus calculator compared to a standard bolus calculator when used for a dinner bolus post exercise (n=14 CSII users) showed a reduction in postprandial LBGI (mean (SD) 2.02 ± 2.63 vs 3.31 ± 2.45; p = 0.006) and percentage TBR <70mg/dL (8.48 ± 11.88% vs 15.18 ± 12.21%; p = 0.049) (210). There was no difference demonstrated in percentage TIR (70-180mg/dL) or TAR (>180mg/dL or >250 mg/dL) (210).

Dassau et al evaluated a novel adaptive artificial pancreas (AP) system in an outpatient single arm non controlled setting (n= 30 included in data analysis). Participants used the Diabetes Assistant (DiAs) smartphone device (University of Virginia). ICR adaptations occurred after

one week followed by weekly basal rate adaptations for 3 weeks and then this pattern repeated over a 12 week period. An algorithm calculated an IS index for each meal using CGM, insulin and meal data and then advised changes to the ICR profile but only in cases of large hypoglycaemic or hyperglycaemic excursions within the preceding 7 days. The Zone Model Predictive controller (MPC) AP (212) adjusted insulin delivery every 5 minutes aiming to keep CGM glucose levels 80-140mg/dL during the daytime with an asymmetric penalty weighted to prevent hypoglycaemia. The Health Monitoring Systems health hypoglycaemia prediction algorithms (213) also ran on the DiAs. Participants gave meal boluses which were adjusted according to their pre-meal SMBG value. Results showed an improved HbA1c with reduced time spent in hypoglycaemia at the expense of hyperglycaemia. HbA1c improved from mean (± SD) 7.0 ± 0.8% at baseline to 6.7 ±0.6% after 12 weeks (-0.3; 95% CI -0.5 to -0.2); p <0.001). percentage TBR improved at all thresholds (<70mg/dL; <60mg/dL; <50mg/dL). percentage TBR<70mg/dL during the daytime improved from 5.0 ± 4.2% during run in to 1.9 ± 2.0% during last week (-3.1; -4.1 to -2.1; p <0.001) and overnight improved from 4.1 ± 4.3% to 1.1 ± 1.9% (-3.1; -4.2 to -1.9; p < 0.001). percentage TAR >180mg/dL increased from 21.1 ±13.5% during run in to 25.5 ± 13.7% at 12 weeks (+4.5 (0.5-8.5); p = 0.027) and mean glucose increased from 141.9±20.1 mg/dL to 152.5 ± 20.7 mg/dL (10.9 (+5.0 to +16.7); p <0.001). Without a control group, it is not possible to ascertain the impact of the bolus and/or basal adaptations exclusively on glycaemic control, in view of the Zone MPC AP algorithm adjusting insulin delivery every 5 minutes and being weighted to prevent hypoglycaemia.

Study evaluating decision support systems in which the insulin modality is not stated

Singla et al (214) described the use of the "T1-Life" android mobile application prototype in which an expert system used rule-based prediction initially to determine insulin doses using the 500 and 1500 rule and then provided weekly recommended adjustments to ICRs based on

a machine learning reinforcement algorithm. The integration of a food database aimed to automate carbohydrate counting. The authors reported preliminary results from 5 children/adolescents (age range 6-20 years old) and did not state whether they were CSII or MDI users (214). An average increase in TIR (70-180mg/dL) of 16.67% was reported for three children who used CGM for the first week as well as the last week (214). The authors did not provide a measure of variance with this result and it is not stated whether the other two children were excluded as they did not wear CGM for the first week. The average TIR (70-180mg/dL) during the last week of app usage was 46.86% (range 39-66%) and TBR (<70mg/dL) was 8.83% (range 2.3-13.6%) (n=5) (214). These glycaemic outcomes appear sub-optimal compared to international consensus recommendations (65), however there is no baseline data reported for comparison. Additionally there appeared to be no standardised protocol and the length of time that each participant used the intervention for ranged from 15 to 36 weeks.

1.5.5 Non-interventional Studies evaluating Decision Support Systems

Nimri et al have also published several non-interventional studies which were surveys of physicians, comparing insulin dose adjustment recommendations between physicians and between physicians and the Advisor Pro (215, 216) or Endo.Digital DSS (ED-DSS) (version 2, DreaMed Diabetes Ltd, Petah Tikva, Israel) (217) (table 3). The ED-DSS (217) functions in a similar way to the Advisor Pro (215, 216) as described above (209). The proportion of full agreement in direction of insulin dose adjustment between physicians was found to be non-inferior to that observed between the Advisor Pro (215, 216) or ED-DSS (217) and physicians for the basal rate, ICR and ISF. All studies demonstrated relatively low levels of agreement in terms of the direction of insulin change amongst physicians, highlighting the diversity of expert's opinions, influenced by their clinical experience. The proportion of full agreement

appeared higher when analysing data cases of pump users with SMBG (216) compared to CGM (215), which the authors postulated may be attributed to the greater volume and complexity of data generated with CGM, leading to higher diversity in decision making. The level of agreement amongst physicians appears lower for adjusting the basal rate for pump users on CGM (mean ± SD) 41 ± 9% (215), compared to 62% ± 14.7% for adjusting the basal dose of MDI users on RT-CGM/isCGM/SMBG (217) (Table 2), perhaps as basal dose changes are more complex in pump users with variable rates throughout a 24 hour period, compared to MDI users on one or two basal insulin doses per day. The magnitude of dose adjustment by the ED-DSS for MDI users was consistently lower than that recommended by physicians due to safety constraints (217) (8%, 14%, 12% by ED-DSS for basal, ICR, ISF adjustments by ED-DSS versus 13%, 33%, 54% by physicians respectively). In pump users, the magnitude of difference in insulin dose adjustment, between physicians and between physicians and the Advisor Pro, was comparable for the basal rate and ICR (215, 216) and ISF in one study (215) but not the other, attributed to outlier data from one physician (216).

1.5.6 Systematic review undertaken

I have conducted a systematic review of adaptive bolus calculators or decision support systems which recommend changes to bolus insulin doses only with Dr Pari Avari as co-reviewer (Appendix 1). Studies were included that evaluated an adaptive bolus calculator or decision support system or algorithms such as run-to-run control, case-based reasoning or other forms of artificial intelligence to recommend changes in insulin bolus doses. Both single arm studies and randomised controlled studies comparing the intervention to a standard bolus calculator or manual bolus calculations were included. Inpatient or outpatient studies in participants with T1D were included and studies were required to report at least one glycaemic outcome. Studies

which recruited both participants with type 1 and type 2 diabetes were excluded, unless the data for those with type 1 diabetes could be extracted. Studies were also excluded if they evaluated a standard bolus calculator only or an adaptive simultaneous bolus and basal calculator, in which case the impact of the adaptive bolus calculator alone could not be ascertained. Studies which predicted blood glucose only, or used decision support to diagnose diabetes, or were performed in silico/simulation, or only described the decision support methods or described a future study were excluded. I undertook searches on Medline, Embase and Web of Science bibliographic databases from date of inception to 13th/14th October 2022 and searched clinicaltrials.gov for recently completed studies. Dr Avari and I independently screened record titles and abstracts from database searches (n=1920), sought reports for retrieval and assessed these for eligibility (n=100), with any disagreements resolved by consensus discussion or by a third reviewer (Professor Nick Oliver). I screened the study entry records identified from the clinicaltrials.gov registry (n=40) and if relevant, retrieved the study entry records to assessed for eligibility (n=27), with exclusions verified by Dr Avari. I extracted data using a standardised form which was checked by Dr Avari. Six studies met the eligibility criteria which have all been included in the above review of decision support systems in this thesis (193, 196, 201, 204, 210, 214). I wrote the draft introduction, methods and results section for the manuscript and Dr Avari wrote the draft discussion and conclusion sections (Appendix 1). The review of decision support systems in this thesis also includes relevant in vivo studies described in the discussion section of the systematic review which adapt both the bolus and basal doses or rates (192, 198, 205, 207, 209, 211).

1.5.7 Summary of Decision Support Systems to date

The majority of the studies described above have demonstrated no overall glycaemic benefit with DSS use, either as single arm or compared to control, for MDI users (198, 204, 205, 207), CSII users (209) or both (201) (table 3). Studies which have shown some glycaemic benefit have had significant study design limitations; only one set of therapeutic recommendations provided prior to a short study period (189), a short observation periods in controlled environments (192, 193, 210), retrospective design with no control group and majority of participants with T2D (206), algorithm only tested for 2 weeks with a fixed diet and initial intentional under-bolusing of insulin (195) or participants usually following low carbohydrate diets (196), no baseline data reported with variable length of intervention use (214) or no control group with a Zone MPC AP algorithm (212) adjusting insulin delivery every 5 minutes and hypoglycaemia prediction algorithms (213) (211). One study demonstrated an improvement in HbA1c with use of the DSS over a 6 month period but participants did not wear CGM and no other glycaemic outcomes were reported (208). There is some evidence that accepting recommendations or actively using the DSS is associated with improved glycaemic control (205, 207). Several studies have compared recommendations by the DSS to physicians (215-217) or physicians have rated the problem detection and case retrieval ability of the DSS (203), but they have not prospectively evaluated the impact of these recommendations or solutions on participants' glycaemic control.

The heterogenous study designs evaluating DSSs makes the comparison of outcomes challenging; the control arm varies from adjustments by a physician (189, 198), CGM with telephone follow up (207), paper log book with usual clinic visits (208), standard bolus calculator (201, 210), standard home insulin therapy (192) or no control group (195, 196, 204-

206, 211, 214). The majority of DSSs present HCP with recommendations for approval prior to implementation (195, 196, 198, 201, 206, 211), with the exceptions of DailyDose (205) and Diabeo (208). The majority of the studies adjust the basal dose in addition to bolus doses (189, 192, 198, 205, 206, 208, 209, 211, 214) and the Advisor Pro also suggests behavioural changes (209), making it more challenging to ascertain the impact of the adjustments to bolus doses alone.

This PhD project evaluates the Advanced Bolus Calculator for T1D (ABC4D), which only adapts bolus doses and this is performed automatically on participants smartphones without requiring physician approval prior to implementation and therefore only requiring periodic oversight. The impact of these adjustments was evaluated prospectively on a range of glycaemic outcomes using CGM in a free-living outpatient setting over a long study duration (8 months, 12 weeks in each treatment period). It is a randomised controlled crossover study using a non-adaptive bolus calculator as control. The next chapters will detail the ABC4D system architecture, study design and methods, results and discussion.

Author, year, name of DSS	Algorithm	Study design	Population	Duration	MDI/CSII	Glucose monitoring	Main results	Comments/limitations
Decision support systems for MDI users								
Reddy et al 2016 Advanced Bolus Calculator for T1D (ABC4D) (204)	Case-based reasoning algorithm Adapts ICRs	Single arm open-label pilot study	N= 10 adults T1D	6 weeks	MDI	SMBG and blinded CGM (iPro 2)	Number of hypoglycaemic episodes (<3.9 mmol/L) < 6 hours postprandial period: median (IQR) 2 (0.5-6.5) in week 6 versus 4.5 (2.0-8.2) in week 1 (p =0.17) Trend suggested reduction in %TBR at various thresholds, increase in %TIR 3.9-10.0 mmol/L with no increase in % TAR >10mmol/L or >15 mmol/L: results not statistically significant in small population size.	
Castle et al 2022 DailyDose (205)	Case-based reasoning algorithm Adapts ICRs, ISFs and basal doses Machine learning algorithms to predict hypoglycaemia	Single arm proof of concept study	N=25 adults T1D	2 week run in, 8 weeks using intervention.	MDI	RT-CGM (Dexcom G6)	No difference in glycaemic outcomes in final 2 weeks of intervention versus 2 weeks baseline. TIR improved by 6.3% in weeks when > 50% recommendations accepted and followed from prior week vs ≤ 50% recommendations accepted. (95% CI 2.5-10.1%; p = 0.001)	No control arm All used Clipsulin to record basal insulin and Inpen with Novolog cartridges to log short acting insulin doses
El Faithi et al 2020 (198)	Run-to-run Learning algorithm adjusts basal dose and ICRs	Randomised parallel study: daily insulin adjustments by learning algorithm (LA) or physician (PA) at summer camp (1:1)	N=21 children and adolescents T1D	11 days	MDI	isCGM (Freestyle Libre)	No difference in TIR (3.9-10.0mmol/L) over last 7 days (LA (39.5% SD 20.7) versus PA (38.4%, SD 15.6); p = 0.89) No difference in number of hypoglycaemic events/day (LA 0.3 IQR (0.1-0.6) versus PA 0.2 (0.0-0.4); p 0.42) LA made 293 adjustments with 92% acceptance rate from physicians	TIR relatively low in both groups, no baseline CGM data Short study duration

							No episodes of severe hypoglycaemia or DKA	
Bisio et al 2022 IN CONTROL Advice (207)	No algorithm information provided Biweekly treatment parameter optimisation routine (not specified if basal and or bolus adaptation in paper). Protocol available from clinicaltrials.gov record (218) (NCT03093636) states that the IN CONTROL Advice optimises basal doses, ISFs and ICRs).	Randomised parallel: G5 and DSS vs G5 (2:1)	N = 80 adults and adolescents >15 years old T1D	14 weeks	MDI	RT-CGM (Dexcom G5)	Within group reduction in HbA1c in both groups compared to baseline (control -0.4%; p=0.009; DSS -0.3%; p = 0.001) Within DSS group, improvement in TIR (+4.4%; p = 0.003), reduction in TBR <60mg/dL (-0.7%; p =0.049) and TAR > 250mg/dL (-3.3% (= 0.01) No between group differences in glycaemic outcomes or patient - reported outcomes Per-protocol analysis: Active users had greater reduction in TBR at all thresholds and in Hypoglycaemia Fear Survey scores compared to non-active users	All transitioned from usual insulin to Degludec and insulin aspart (smartpens).
Bode et al 2018 Glytec CDSS (206)	Glytec CDSS software (no further information provided) Adjusts basal and/or bolus doses	Quality improvement project with before and after design	N = 46 clinic patients 76% T2D	Training period 90 days then project ran for further 11 months	MDI	SMBG	Reduction in HbA1c from baseline to 12 months (10.2% versus 7.2%, p < 0.00001)	No control group Retrospective design Majority T2D High baseline HbA1c as referred by HCP into clinic to improve glycaemic control
DSS for combined study populations of CSII and MDI users								
Avari et al 2021 PEPPER system (201)	Case-based reasoning Adapts bolus doses and “carbohydrate correction factor” to correct hypoglycaemia	Randomised controlled crossover study: PEPPER versus control (standard bolus calculator)(1:1)	N = 54 adults (Intention to treat analysis) T1D	8 months (4 week run in, 12 weeks in each treatment phase separated by 3-4 week washout period)	MDI/CSII	RT-CGM (Dexcom G5)	No significant difference in glycaemic outcomes or measures of glycaemic variability PEPPER versus control, for example % TIR 3.9-10.0mmol/L (median (IQR) 62.5% (52.1-67.8) versus 58.4 (49.6-64.3); p=0.27)	Higher perceived frequency of hypoglycaemia PEPPER versus control (p = 0.03) without an objective difference in % TBR between groups

Charpentier et al 2011 Diabeo (208)	Automatic algorithms for adjustment of ICR and basal dose/rate	Randomised parallel: usual quarterly visits (control) (G1); Diabeo and quarterly visits (G2); Diabeo and teleconsultations (G3)	N = 180 adults T1D	6 months	MDI/CSII	SMBG	Difference in HbA1c reduction significant between G1 and G2 (0.67% (0.35-0.99); p <0.001) and between G1 and G3 (0.91% (0.60-1.21); p <0.001) but not between G2 and G3.	
Breton et al 2018 UVA Decision Support System (192)	Net effect re-simulation and optimisation Adapts ICRs, ISFs and either basal rate patterns (CSII) or total dose and timings for MDI	Randomised cross-over: control/ experimental admissions	N =24 adults and adolescents (>= 17 years of age) T1D	2 x 48 hour outpatient admissions separated by 4 weeks	MDI/CSII	SMBG (and blinded Dexcom G4 unless participant already using CGM as standard care)	DSS compared to control: Reduction in daytime glycaemic variability (co-efficient of variation DSS 0.33 ±0.06 vs control 0.36 ± 0.08 vs p = 0.045) Reduction in % TBR <70mg/dL (DSS 0.9% (0.4% - 2.3%) versus control 3.2% (1.3% to 4.8%); p = 0.018)	Short observation periods in a controlled environment
DSS for CSII users								
Schwartz et al 2008 (202)	Case-based reasoning	Single arm study to build case base: every week physicians identified new problems, recommended therapeutic adjustments and contacted participants. Knowledge engineers structured findings into cases and updated the casebase later following review of the effectiveness of these recommendations.	N=20 T1D	6 weeks	CSII	SMBG and CGM for weeks 1,3,6	50 cases of individual patient problems with their solutions and outcomes were identified, grouped into 12 different types of clinical problems. Engineers developed software to detect these 12 types of clinical problems automatically. Data rescanned and software detected average of 29 occurrences of the 12 different clinical problem types per participant over the study period (average 4.9 problems per participant per week)	High drop out rate (8 out of 20): participants cited lack of time to enter data or personal issues as reasons. Participants felt time required to document life events was burdensome.

Schwartz et al 2010 4 Diabetes Support System (203)	Case-based reasoning No detailed information provided regarding the therapy adjustments proposed in solutions	Single arm study to assess ability of DSS to detect problems correctly (evaluated by physician weekly) and evaluate case retrieval module (once study completed)	N=26 adults T1D (N=23 completed study)	5 weeks	CSII	SMBG CGM in 6 out of 23	System detected total of 295 possible problems, of which were reviewed by participants' personal physicians: Physicians deemed 97.7% were correct and 2.1% were incorrect. Physicians rated 96.1% clinically useful, 3.2% not useful, 0.7% possibly useful. System detected on average 12.8 problems per participant over 5 weeks (equivalent to 2.6 problems per participant per week) Overall system retrieved a matching case with beneficial solution 82% of time.	No glycaemic outcomes
Zisser et al 2005 (195)	Run-to-run control Adapts ICRs and timings of dose	Single arm study	N=14 adults T1D	10 weeks (phase 5: 1 week when algorithm adapted lunch ICR only and phase 6: 1 week when algorithm adapted ICR for all 3 meals)	CSII	SMBG	Improvement in HbA1c (final 5.6 ± 0.2% versus baseline 6.5 ± 0.7%; $p < 0.003$) Subject meal-responses categorised into: Class A: convergent within 3-4 days within target range Class B: remained in target range Class C: divergent from target range Phase 5: 33% class A, 33% class B and 33% class C/incorrect sensitivities and/or mitigating circumstances. Phase 6: 41% class A, 26% class B, 33% class C/incorrect sensitivities and/or mitigating circumstances	Food prepared by professional chef in collaboration with dietitian. Routine snacks not permitted (only to treat hypoglycaemia) Intentional underbolusing of insulin (and also late bolus in phase 5) to induce postprandial hyperglycaemia High drop out rate (5 out of 14)
Zisser et al 2009 (196)	Run-to-run control Adapts ICRs	Single arm study	N=9 adults T1D	6 weeks (last 2 weeks of testing of	CSII	SMBG	1 hour postprandial BG level (mean ± SD) 104 ± 19 mg/dL	"Convergence" defined as first day

				run-to-run algorithm for 3 meals/day)			2 hour postprandial BG levels (96.5 ± 18 mg/dL) approached pre-prandial levels (90.1 ± 13 mg/dL). 12 hypoglycaemic measurements (<55 mg/dL) over 230 meals (mean 45.0 ± 5.0 mg/dL). No severe hypoglycaemic episodes. Difference in 1 hour postprandial BG levels between the period before and after convergence (p= 0.013, p = 0.023, p = 0.0018 for breakfast, lunch, dinner respectively).	that postprandial BG targets achieved. Participants could vary CHO content of meals but usually followed low CHO diets. No results regarding average amount of CHO consumed for each meal.
Anderson et al 2016 Pumptune (189)	Modified PID controller algorithm: "glucose concern score" used to optimise insulin by recommending changes to ICR, ISF or basal rate proportionate to their predicted contribution to each hour's insulin activity	Randomised crossover study: setting adjusted by Pumptune (intervention) or physician (control) prior to each study period	N=22 children aged 6-14 years T1D	2 study periods each of 6.5 days	CSII	SMBG and blinded CGM (iPro 2)	Pumptune settings associated with greater % TIR (3.9-10.0mmol/L) than physician settings (mean (SD) 64.3 (9.7)% versus 57.4 (11.4)%; p = 0.016) and lower % TAR > 10mmol/L (26.9 (9.6)% versus 33.5 (13.6)%; p = 0.021) No difference in %TBR <3.9 mmol/L	Well controlled study population; baseline HbA1c mean 57 mmol/mol (7.4%). Majority female participants (69%) Only one set of recommendations given prior to each study period
Nimri et al 2020 Advisor Pro ADVICE4U study (209)	Recommends adjustments to basal insulin infusion rate, ICR, ISF. Also provides personalised diabetes management advice regarding the way insulin is delivered.	Multinational, parallel, non-inferiority, randomised controlled study (1:1 to receive remote insulin adjustment by AI-DSS or physicians)	N= 108 (ITT analysis) children, adolescents and young adults (aged 10-21 years) T1D	6 months	CSII	CGM	% TIR (3.9-10.0mmol/L (70-180mg/dL)) within AI-DSS arm statistically non-inferior to physician arm (50.2% ± 11.1% versus 51.6 ± 11.3%); p <$1X10^{-7}$) % TBR <3.0 mmol/L (<54 mg/dL) within AI-DSS arm statistically non-inferior to physician arm (1.3 ± 1.4% versus 1.0± 0.9%; p < 0.0001) No difference in HbA1c change between 2 arms (p = 0.49)	Recommendations by AI-DSS presented to physician who could approve/modify recommendations

							3 SAEs; 2 severe hypoglycaemia, 1 DKA in physician arm, none in AI-DSS arm	
Bell et al 2016 (193)	Adaptive Model-Predictive Bolus (MPB) algorithm	Randomised controlled cross-over: low fat low protein (LFLP) or high fat high protein (HFHP) meals consumed using ICR and 50%/50% combination bolus over 2 hours. On subsequent admissions, MPB algorithm recommended optimal dose, split and duration for HFHP meal and visits repeated until set glucose criteria reached.	N=10 adults T1D	3-6 study day admissions	CSII	YSI glucose analyser from venous blood samples	MPB algorithm achieved glucose set targets at first visit (n=7), initial MPB too high (n=2) and too low (n=1) requiring additional 2-3 visits. HFHP meal: MPB algorithm compared to 50/50% combination bolus over 2 hours decreased incremental area under the curve (11,712 ± 3172 mg/dL min vs 27,092 ± 1709 mg/dL min; p = 0.0013) and incremental change in blood glucose concentration (24 ± 11 mg/dL vs 73 ± 4 mg/dL; p =0.001)	Short admissions in a controlled environment
Fabris et al 2020 Diabetes Assistant (DiAs) smartphone platform (University of Virginia) (210)	Algorithm uses CGM and pump data and a glucose-insulin dynamics model included within an optimally tuned Kalman filter to dynamically estimate the insulin sensitivity (IS) index	Randomised controlled crossover: post exercise dinner bolus calculated using standard bolus calculator (control) or IS-informed smart bolus calculator (intervention)	N=15 adults (data from n= 14 included in analysis) T1D	4 week data collection period then 2 x 24 hour hotel admissions (at least 48 hours apart)	CSII	RT-CGM (Dexcom G6)	IS informed bolus calculator compared to standard bolus calculator reduced postprandial a) LBGI (2.02 ± 2.63 vs 3.31 ± 2.45; p = 0.006) b) TBR <70mg/dL (8.48 ± 11.88% vs 15.18 ± 12.21%; p = 0.049) No difference in postprandial %TIR (70-180mg/dL) or %TAR (>180mg/dL or <250mg/dL)	Short admissions in a controlled environment
Dassau et al 2017 Diabetes Assistant (DiAs) smartphone device (University of Virginia) (211)	Pattern of ICR adaptation then weekly basal rate adaptations for 3 weeks. Zone MPC AP (212) and Health Monitoring System hypoglycaemia prediction algorithms (213)	Outpatient single arm controlled multicentre study	N=30 adults included in data analysis T1D	15 weeks (1 week SAP device training, 1 week SAP run in, 1 week ICR adaptation and AP run in, 12 weeks intervention)	AP	CGM (Dexcom G4)	Improvement in HbA1c from mean (± SD) 7.0 ± 0.8% to 6.7 ±0.6% after 12 weeks (-0.3; 95% CI -0.5 to -0.2); p <0.001) %TBR <70mg/dL daytime decreased from 5.0 ± 4.2% during run in to 1.9 ± 2.0% during last week (-3.1; -4.1 to -2.1; p <0.001) and overnight decreased from 4.1% ± 4.3 to 1.1% ± 1.9 (-3.1; -4.2 to -1.9; p < 0.001)	No control arm

							No change in %TIR 70-180mg/dL Increase in %TAR >180mg/dL from 21.1 ±13.5 run in to 25.5 ± 13.7 at 12 weeks (+4.5 (0.5-8.5); p = 0.027) Increase in mean glucose 141.9±20.1 mg/dL to 152.5 ± 20.7 mg/dL (10.9 (+5.0 to +16.7); p <0.001)	
DSS in which insulin modality not stated								
Singla et al (214) "T1-Life" android mobile application	Initial prediction rule based (500 and 1500 rule) then weekly ICR adjustments recommended based on machine learning reinforcement principle. Food database automated carbohydrate counting.	Single arm pilot interventional open label	N=5 children/adolescents (range 6-20 years of age)	15-36 weeks (variable per participant)	Not stated	SMBG and blinded CGM (Abbott Libre Pro)	Last week of use: Average TIR (70-180mg/dL) 46.86% (range 39-66%) (n=5) Average TBR <70mg/dL 8.83% (range 2.3-3.6%) (n=5) TIR 70-180mg/dL increased by average of 16.67% in n=3 who used CGMS in 1st and last week	No baseline glycaemic data provided No standardised protocol
Non-Interventional Studies								
Nimri et al 2018 Advisor Pro (215)	Recommends insulin therapy adjustments (basal dose and bolus ICR/ISF) and provides personalised behavioural recommendations	Survey of physicians Compares insulin dose adjustment recommendations amongst physicians and between Advisor Pro and physicians (non-inferiority)	N=26 physicians N= 15 datacases of children/young adults T1D	3 weeks of data	CSII	CGM	Proportion of full agreement on direction of insulin dose adjustment amongst physicians non-inferior to that observed between Advisor-Pro and physicians (41 ± 9%, 45 ± 11% and 45.5 ± 13% for basal rate, ICR, ISF respectively amongst physicians versus 41.5± 8 %, 48 ±11 %, and 43.5±11 for basal rate, ICR, ISF respectively between Advisor Pro and physicians; p < 0.01 for all 3 parameters)	Advisor Pro designed for use by HCP No real-time advice

							Magnitude of dose adjustment by Advisor Pro at least equal to or less than that recommended by physicians	
Nimri et al 2020 Advisor Pro (216)	Recommends insulin therapy adjustments (basal dose, ICR/ISF) and provides personalised behavioural recommendations	Survey of physicians Compares insulin dose adjustment recommendations amongst physicians and between Advisor Pro and physicians (non-inferiority)	N=17 physicians N=15 datacases of adolescents/young adults T1D	3 weeks of data	CSII	SMBG Pump	Proportion of full agreement on direction of insulin dose adjustment amongst physicians non-inferior to that observed between Advisor-Pro and physicians (51.8 ± 9.2%, 54.2 ± 6.4% and 49.8 ± 11.6% for basal rate, ICR, ISF respectively amongst physicians versus 49.5± 6.4 %, 55.3 ±8.7%, and 47.6±14.4 for basal rate, ICR, ISF respectively between Advisor-Pro and physicians; p= 0.01 basal rate, p = 0.002 ICR, p <0.001 ISF) Mean absolute difference in magnitude of change (in cases of full agreement in direction of changes) between physicians and between Advisor-Pro and physicians comparable for basal rate (p < 0.001) and ICR (p <0.001); non-significant for ISF attributed to outlier data from one physician.	Advisor Pro designed for use by HCP No real-time advice
Nimri et al 2022 Endo.DigitalDSS (ED-DSS) (217)	Recommends insulin therapy adjustments (basal dose and bolus ICR/ISF) and provides personalised behavioural recommendations	Survey of physicians Compares insulin dose adjustment recommendations amongst physicians and between ED-DSS and physicians (non-inferiority)	N =20 physicians N = 17 datacases (mean (± SD) age 35.0 ± 18.0 years) T1D	3 weeks of data	MDI	RT-CGM/isCGM and/or SMBG	Proportion of agreement on direction of insulin dose adjustment amongst physicians non-inferior to that observed between ED-DSS and physicians (62.0 ± 14.7%, 48.6 ± 14.6%, and 49.6 ± 14.7% for basal rate, ICR, ISF respectively amongst physicians versus 67.6 ± 14.7%, 55.0 ± 15.2%, and 58.3 ± 13.7% for basal rate, ICR, ISF respectively between ED-DSS and physicians; p < 0.001 all 3 parameters)	ED-DSS designed for use by HCP No real-time advice

							Magnitude of change consistently lower ED-DSS versus physicians.	

Table 1.3: Summary of Recent Decision Support Systems

Abbreviations: Artificial intelligence (AI); artificial pancreas (AP); blood glucose (BG); continuous glucose monitoring (CGM); carbohydrate (CHO); continuous subcutaneous insulin infusion (CSII); diabetic ketoacidosis (DKA); decision support system (DSS); healthcare provider (HCP); insulin-to-carbohydrate ratio (ICR); intermittently scanned continuous glucose monitoring (isCGM); insulin sensitivity factor (ISF); intention-to-treat analysis (ITT); learning algorithm (LA); multiple daily injections (MDI); model predictive controller (MPC); proportional-integral-derivative (PID); real-time continuous glucose monitoring (RT-CGM); severe adverse event (SAE); self-monitoring of blood glucose (SMBG); time above range (TAR); time below range (TBR); time in range (TIR); Type 1 diabetes (T1D)

Chapter 2: System Architecture

2.1 Introduction

The Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) study was an 8-month randomised controlled crossover study to evaluate an adaptive decision support system for insulin bolus adjustment in MDI users. The integrated ABC4D system consisted of a real-time insulin bolus calculator displayed on a smartphone application used with real-time continuous glucose monitoring (RT-CGM) and a web-based clinicians' platform for monitoring purposes. The ABC4D app ran in either adaptive bolus calculator mode (ABC4D; intervention) or non-adaptive bolus calculator mode (control).

My role included the day to day running of the study, conducting study visits, setting up the bolus calculator app for participants at the start of the control and intervention phases and being the first point of call for participants throughout. I reviewed submissions and glucose data on the clinician's platform and chaired bimonthly meetings with the engineers to troubleshoot any issues observed or raised by participants. I analysed the data for all the participants with assistance from Ryan Armiger (engineer), as outlined in chapter 3 (section 3.9).

The contents of this chapter and chapter three have been summarised in a manuscript submitted to the Diabetes Technology and Therapeutics journal (accepted for publication) (219).

2.2 ABC4D smartphone application

Participants used the ABC4D app on an iPhone (Apple Inc, Cupertino, CA, USA); either their own personal iPhone or a study iPhone if required. The ABC4D app ran as an adaptive (intervention) or non-adaptive (control) bolus calculator. Participants were blinded to treatment group. The research team were able to switch from one mode to the other remotely. The adaptive and non-adaptive bolus calculator were identical in terms of input screens, mandatory/optional information for participants to enter and the factors adjusting the dose recommendation. The difference was that the ICR and consequently ISF were adjusted automatically throughout the intervention phase (adaptive bolus calculator) using a case-based reasoning algorithm (described in section 2.1.5), whereas these settings would remain the same throughout the control phase (non-adaptive bolus calculator). All of the following described features were applicable to both the adaptive and non-adaptive bolus calculator.

The following information was required for each insulin dose recommendation displayed on the smartphone application;

- Time of day
- CGM glucose value
- Meal carbohydrate value
- Exercise (recent or planned)

Figure 2.1 shows the ABC4D app interface for insulin dose advice. Once a participant had provided the aforementioned input information and pressed “advice”, the “insulin recommended” page appeared which displayed the recommended dose with the breakdown

detailed underneath. Participants could override the dose recommendation if they wished, select dual bolus and or write a comment and then press “accept” to save the submission.

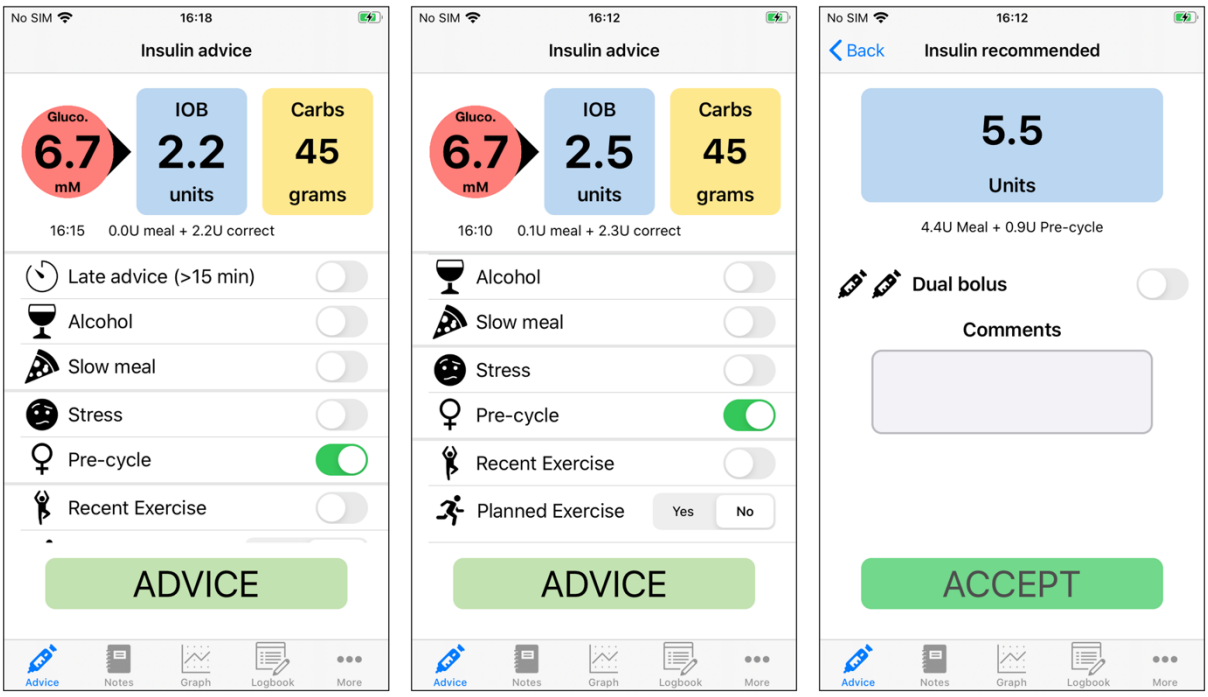


Figure 2.1: ABC4D app interface for insulin dose advice

Reproduced with permission from Unsworth et al (219)

The time of day and CGM glucose value were automatically gathered; participants were required to enter the carbohydrate amount and select yes or no to planned exercise (mandatory) or select recent exercise if applicable (optional). “Planned exercise” was defined as exercise participants were planning to do within the next 2 hours after the bolus injection. If participants selected yes to planned exercise, they could then enter details about the type (aerobic/anaerobic/mixed), intensity and duration of exercise to be undertaken. Once a participant had submitted an insulin dose recommendation with planned exercise selected, “recent exercise” was automatically selected for the following 8 hours. Participants could inactivate this if they wished. Participants could also select “recent exercise” independently without having selected “planned exercise” for a prior submission.

Late advice (>15 minutes) was a safety feature designed for when participants were requesting an insulin dose recommendation >15 minutes after a meal. It only recommended insulin to cover the meal and no correction insulin or additional insulin for the positive rate of change adjustment, to reduce the risk of subsequent hypoglycaemia.

The "pre-cycle" function could be selected manually by participants or activated automatically. Automatic activation was based on menstrual cycle length entered into the platform settings at app initiation and first day of their last menstrual period entered by participants into the app.

Participants could also select the following parameters which were useful for the clinician reviewing the data on the platform but did not change the insulin dose recommendation; alcohol, slow meal or stress. If participants wished to split an insulin dose, for example with meals that were high in fat, they were advised to select dual bolus and then write a comment as to how they were going to split it.

Participants were able to view a breakdown of the recommended insulin dose which was rounded to the nearest 0.5 units. This was displayed as:

a) Insulin to cover the meal/snack
b) Correction dose insulin minus any correction insulin already on board from previous correction doses
c) Rate of change (ROC) adjustment: Insulin added if sensor glucose was increasing rapidly or subtracted if sensor glucose was decreasing rapidly (modified from Aleppo et al (220))

d) Menstrual cycle adjustment ("pre-cycle")

Participants could submit a comment along with the insulin dose if they wished, which was visible to the research team on the clinician's web platform. Participants were advised that if did not agree with the insulin dose recommended, to override it by deleting the number, typing the number of units they wished to take instead and pressing submit.

A safety pop up was developed if a positive rate of change in glucose levels was detected, to check if it was a late dose or the participant had just treated a hypo. If a participant then selected "yes", the algorithm would not add any correction dose insulin or additional insulin to adjust for the positive rate of change in glucose levels.

Notes

In the notes tab of both the adaptive and non-adaptive bolus calculator app, participants were able to select illness, jetlag/sleeplessness or change in basal insulin (Figure 2.2). If a participant selected illness, all the submissions for the rest of the day until 00:00 would be automatically excluded from the case base if the app was running in the adaptive bolus calculator mode. Participants were also able to submit a comment which could be seen by the research team on the web-based platform (Figure 2.2).

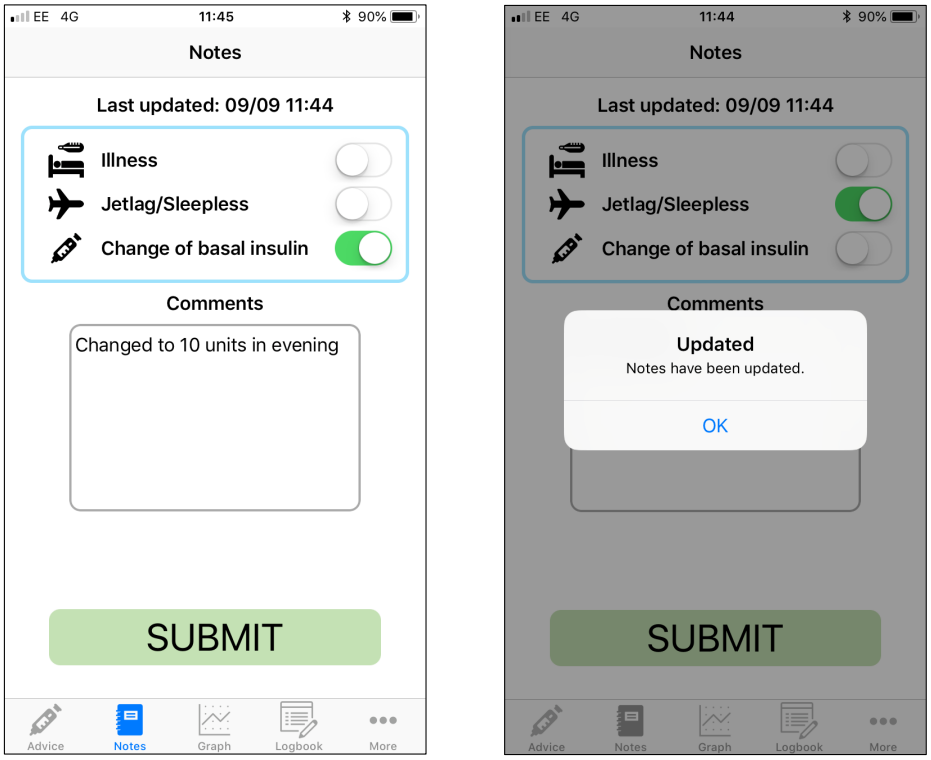


Figure 2.2: ABC4D app notes tab

Graph and logbook

Participants were able to view a graph of their glucose levels since 00:00 that day with their submissions represented by circles in both the adaptive and non-adaptive bolus calculator (Figure 2.3 a). The variable high glucose set point was represented by a grey dotted line. The high glucose setpoint increased after meals and then decreased over time back to baseline (6.7 mmol/L). The low glucose setpoint was fixed at 4.5 mmol/L. Participants could view their insulin dose submissions in the logbook tab (Figure 2.3 b).

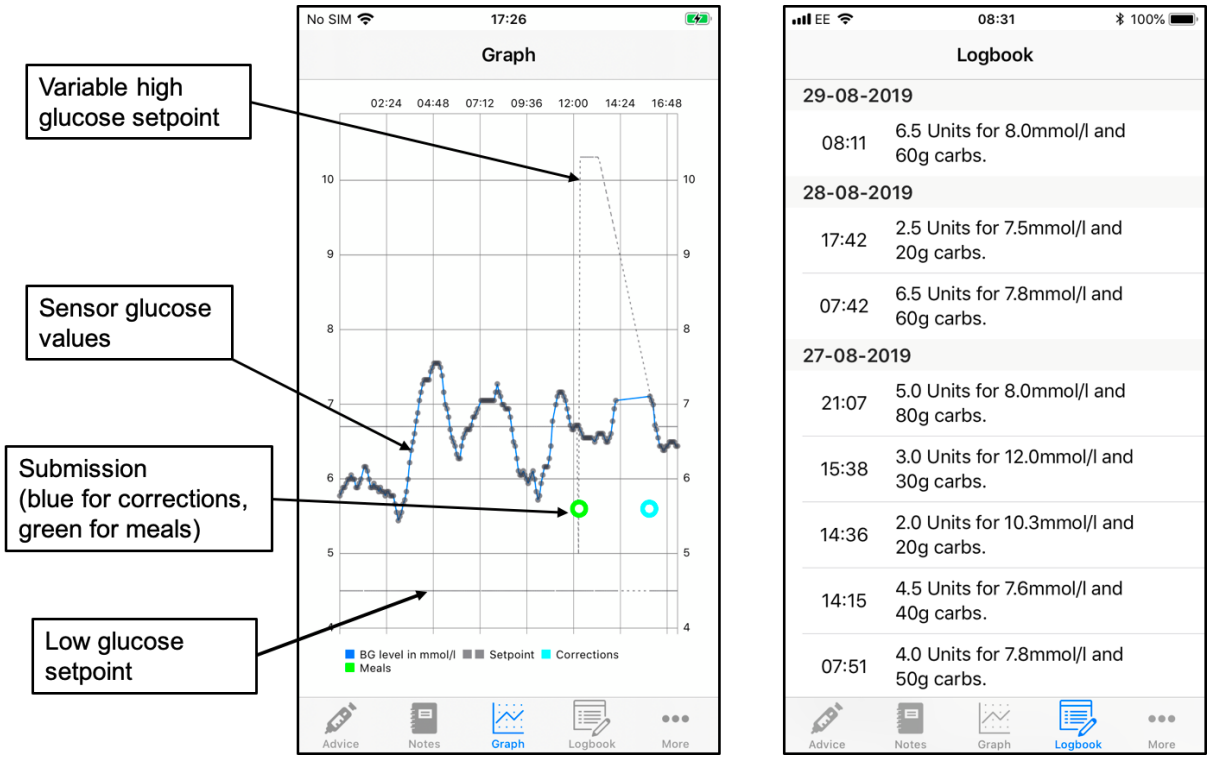


Figure 2.3: The ABC4D app a) graph and b) logbook

2.3 Insulin bolus calculation

Both the adaptive and non-adaptive bolus calculator apps used the following formula to calculate the insulin bolus dose:

Bolus dose = meal insulin + correction insulin – correction insulin on board + glucose rate of change adjustment

Meal insulin = amount of carbohydrates to be consumed/ICR

Correction insulin = (Current glucose level[1] - high glucose setpoint)/ISF

[1]current glucose level from sensor glucose level automatically imported or manually entered SMBG value (for example during sensor warm up period)

Abbreviations: insulin-to-carbohydrate ratio (ICR), insulin sensitivity factor (ISF)

The high glucose set point is variable during the postprandial period (Figure 2.3 a (The ABC4D app graph). If the glucose level was above this high glucose set point when requesting insulin dose advice, the algorithm would correct down to this set point.

The formula used for both the adaptive and non-adaptive bolus calculator adjusted the dose recommended for exercise, glucose rate of change (modified from Aleppo et al (220)) and menstrual cycle. The same insulin dose reduction was applied regardless of the type, duration or intensity of planned exercise and the same dose reduction was applied for both planned and recent exercise. During the control arm, selection of "planned" or "recent exercise" applied a 30% reduction to the bolus dose recommended. At the start of the intervention arm, initial ICRs were calculated which led to a 30% reduction in the meal insulin dose and these then adapted over the intervention period. The menstrual cycle ("pre-cycle") feature offered an optional 20% increase in bolus doses in the 7-day window prior to predicted menstruation. Recent basal insulin was not considered by either the adaptive or non-adaptive bolus calculator.

2.4 Initial Settings

Insulin-to-carbohydrate ratios and insulin sensitivity factor

The ICRs for each meal entered at the start of the control/intervention phase were those which the participant had been using prior to the visit during the run in or washout phase. The timeframes for each mealtime were personalised. The ISF entered at the start of the control arm was the same as the participant had been using prior to the visit, unless there was evidence on CGM data review of recurrent hypoglycaemia following correction doses, in which case this was deemed a safety issue and a less aggressive ISF was entered if the participant was in

agreement. In the intervention arm, the ISF (correction factor) was assumed to be correlated with ICR as described by King et al (221) below. This assumption was necessary for the ICR adaptation mechanism.

Correction factor (mg/dL/unit)= 4.44 * ICR (g/unit) ($r = 0.9$, $p < 0.0005$) (221)

Then converting into mmol/L:

Correction factor (mmol/L/unit) = 4.44/18 * ICR (g/unit)

For example, if the ICR was 1unit:5g

ISF = 4.44 * 5 = 1.23 mmol/L/unit

1 unit of insulin brings down the blood glucose by 1.23 mmol/L

Feedback from the first cohort of participants recruited before the covid-19 pandemic included that the correction doses were sometimes much larger than they would usually take. This was due to a large ICR/ISF mismatch in the adaptive arm using the above formula (221). Therefore for the second cohort of participants recruited remotely, an optional 10% increase in ICR entered at baseline could be applied if there was evidence of a large ICR/ISF mismatch which would lead to significantly higher correction doses than the participant would usually take, as long as the participant was in agreement with the 10% increase in ICR. An example taken from the study is provided below.

Participant's usual ICR for lunch is 1unit:5g Corresponding ISF = (4.44/18) X 5 = 1.23 mmol/L/unit i.e 1 unit reduces blood glucose by 1.23 mmol/L However participant's usual ISF is 1 unit reduces blood glucose by 3.0- 4.0 mmol/L therefore large ICR/ISF mismatch.
As large ICR/ISF mismatch, multiply ICR by 1.1 Usual ICR 1:5g 10 X 1.1= 1:5.5g
New ISF with adjusted ICR (1:5.5g) ISF = (4.44/18) X 5.5 = 1.36 mmol/L/unit 1 unit reduces BG by 1.36 mmol/L (less aggressive than 1 unit reduces blood glucose by 1.23 mmol/L if use ICR 1:5g and slightly closer to that which the participant had been using prior to the treatment phase (1 unit reduces blood glucose by 3.0-4.0 mmol/L))

Participants were advised to override doses if they thought they were still too high. Participant were also advised to override doses if they thought they were too low, which the meal doses may then have been if the ICR had been increased by 10% and their pre-meal blood glucose was in target range.

Exercise ICRs for the intervention arm

At the start of the intervention arm, ICRs were calculated for exercise cases which resulted in a 30% reduction in meal doses which then adapted over the course of the treatment phase. The following formula was used:

Exercise ICR = usual meal ICR /0.7

Example: usual ICR 1unit :10g

Exercise ICR = 10/0.7 = 14.3 g/unit

2.5 The ABC4D web-based clinicians' platform

I sent the settings from the ABC4D web-based clinicians' platform to participants' smartphones at the start of each treatment period. The platform displayed graphs of glucose levels and submissions for each participant over the selected date range (Figure 2.4). The details of each submission were also visible to the research team (Figure 2.5). The research team were able to visualise the evolution for each participant in the intervention phase. Every 2 weeks, I reviewed the glucose levels, submissions and notes submitted for both the control and intervention arms on the clinical platform. For participants in the adaptive arm, I reviewed the new proposed ICRs and the evolution. I updated the engineers with any issues observed by myself or reported by participants. The engineers investigated these and released software updates when required to debug the system. A list of software updates is provided in the next chapter.

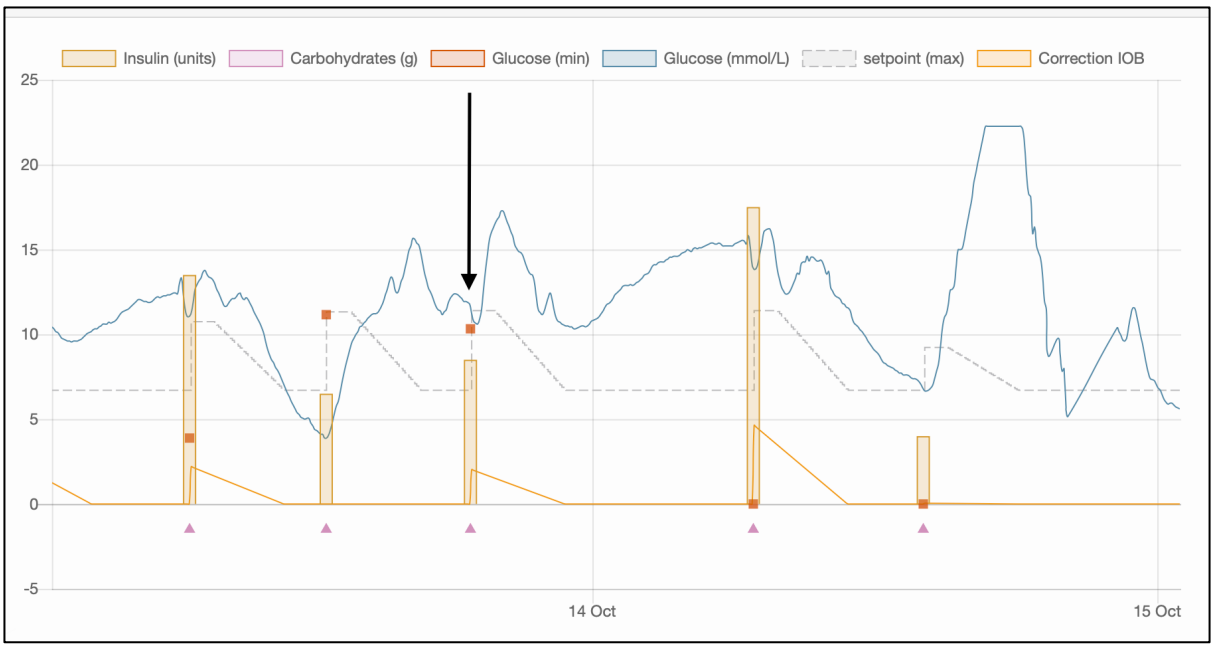


Figure 2.4: A screenshot of a graph displayed on the ABC4D clinicians' web-based platform

The blue line represents the participant's glucose levels. The yellow vertical bars represent the insulin doses taken. The purple triangles represent when the submission includes an amount of carbohydrate (meal or snack rather than solely a correction dose). The orange line is the correction insulin-on-board. The grey dotted line represents the variable high glucose set point. The orange squares represent the minimum glucose level in the 2-6 hour postprandial window.

USERNAME	TIMESTAMP	LOCALTIME	SUBMISSION TYPE	GLUCOSE	GLUCOSE ROC	CARBOHYDRATES	MEAL IOB	CORRECTION IOB
ABC5013	October 13th, 2020, 5:49 pm	13 18:49:08 +0100 | 1.9.12	Dinner	11.80	-0.01	65.00	0.00	0.00

INSULIN TO CARB RATIO	INSULIN TO SENSITIVITY RATIO	INSULIN REDUCTION ROC	INSULIN TOTAL	INSULIN USER	INSULIN MEAL	INSULIN CORRECTION
9.98	2.46	0.00	8.50	8.50	6.45	2.05

GLUCOSE MINIMUM TIME	GLUCOSE MINIMUM	HIGH GLUCOSE SETPOINT	NEW INSULIN TO CARB RATIO	NEW SATURATED INSULIN TO CARB RATIO	REASONS FOR AUTOMATIC REJECTION
October 13th, 2020, 10:12 pm	10.32	6.70	8.59	8.59	None

Figure 2.5: Details visible on the clinicians' web-based platform

These details refer to the submission marked with a black arrow in Figure 2.4 above.

This was displayed horizontally on the platform and has been split into 3 segments for the purpose of inclusion here. The minimum glucose level (10.3 mmol/L) is above the high glucose setpoint (6.7 mmol/L), therefore the new insulin to carbohydrate ratio is more aggressive (8.59 g/unit compared to the initial ICR of 9.98 g/unit).

Abbreviations: Rate of change (ROC)

2.6 ABC4D algorithm

Development of the ABC4D algorithm

The ABC4D system architecture has previously been described in detail by Herrero et al (222) and Pesl et al (223). The algorithm used in ABC4D employs run-to-run (R2R) and case-based reasoning (222). The run-to-run principle is that each day is considered a run and the ICR for each meal is adapted daily dependent on a performance measure, based on the postprandial glucose excursion from the previous day (194). This process is continued until the algorithm converges within a set glucose target range after a set period or number of runs (195). However there are several limitations to the run-to-run control algorithm; it only differentiates between three meals (breakfast, lunch and dinner) and it assumes the insulin therapy and daily routines of an individual are repetitive which is unrealistic for many in a real-world setting (222). Additionally early testing relied on two capillary blood glucose samples to assess the postprandial excursion (194) which may not capture the varying postprandial responses following meals of mixed composition (222). Therefore, Herrero et al proposed a novel version of the R2R algorithm which adjusted the ICR based on CGM area under the curve (AUC) data rather than two fingerpick glucose values (222). Whilst this algorithm offers more flexibility in terms of meal composition, it is limited by variations in insulin sensitivity within the same individual, such as after exercise (222). A proposed solution to this is to use multiple R2R incidences for each possible situation (case) encountered (such as breakfast with exercise) by employing a case-based reasoning technique (222). Additionally the R2R algorithm used to adjust the ICR based on the CGM AUC (222) was an early metric; the algorithm employed in this study used the postprandial minimum glucose level instead.

The case-based reasoning algorithm is based on four steps: retrieve, re-use, revise and retain (199, 222, 224). The algorithm defines the problem using parameters which could potentially impact blood glucose levels, such as time of day and exercise (224). It then retrieves a similar case and re-uses a previously revised solution (ICR and ISF) (224). The algorithm then reviews whether the minimum post prandial glucose level at 2 - 6 hours (outcome) is within target to decide if an adaptation is necessary, revises the solution (ICR) accordingly and retains the revised ICR in the case base (Figure 2.6). The ISF consequently also changes as it is based on the previously described formula by King et al (221).

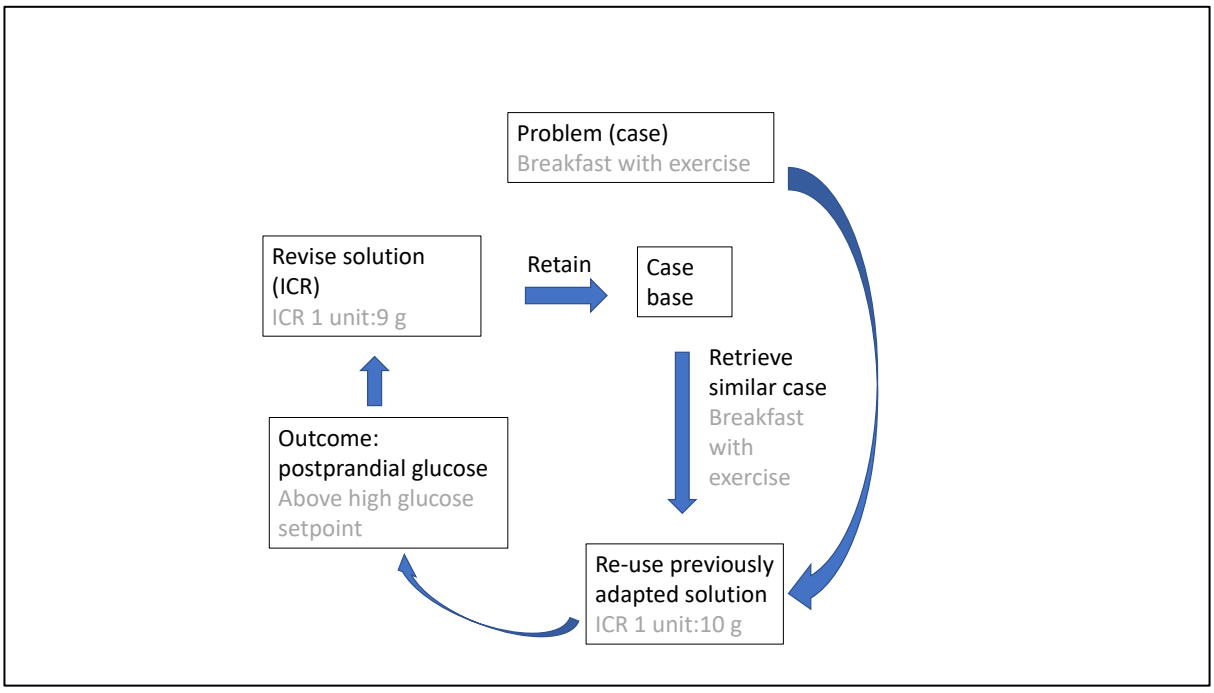


Figure 2.6: Case-Based Reasoning cycle applied in the ABC4D study, as described by Aamodt et al (199) and Pesl et al (200).

The grey text illustrates an example.

Abbreviations: grams (g)

In silico testing of the case-based reasoning (run-to-run) (CBR (R2R)) algorithm compared to the stand alone run-to- run algorithm, demonstrated improved mean blood glucose in the adult population from 166 ± 39 mg/dL to 150 ± 16 mg/dL respectively ($p = 0.03$) and in the adolescent population from 167 ± 25 mg/dL to 162 ± 23 mg/dL ($p = 0.06$) (222). In addition,

the CBR(R2R) algorithm was able to completely eliminate hypoglycaemia (<70mg/dL) which the standalone R2R algorithm was unable to do in the adolescent population (222).

Use of the run-to-run case-based reasoning algorithm in the ABC4D study

There were 6 cases used in this study: breakfast, lunch and dinner with exercise and without exercise. The timings for these meals were personalised for each participant. The CBR algorithm revised the ICR for each submission if required and proposed a new ICR. The new proposed ICR was calculated based on the postprandial minimum glucose value in the 2-6 hour window after a meal. An example of a new proposed ICR is provided in Figure 2.6. The high glucose setpoint was variable and increased after a meal, decreasing to 6.7 mmol/L when fasting.

The median of the new proposed ICRs for 3 submissions for a particular case (ICR_b) was used with the initial ICR (ICR_a) to calculate a mean average ICR (ICR_c). The case base adaptations were automatic and performed locally on participants' smartphones at 04:00 every day. Data were uploaded to the clinicians' platform at this time if connected to wifi. Table 2.1 shows a theoretical example of the case base evolution process for conceptual purposes. The next time a participant selected that case (for example breakfast with exercise), the new ICR (ICRc) would be employed in the algorithm. The ICR changes were saturated to +/- 20% due to safety constraints.

Case: breakfast with exercise Initial ICR (ICR_a) 1 unit:10g	Postprandial glucose	New proposed ICR
Day 1	Above high glucose setpoint	1:8 g
Day 2	Above high glucose setpoint	1:9g
Day 3	Below the low glucose setpoint	1:11g
Median of new proposed ICRs (ICR_b)	-	1:9g
ICR updated in the case base (ICR_c) $ICR_c = (ICR_a + ICR_b)/2$	-	1:9.5g

Table 2.1: A theoretical example for illustrative purposes of the ICR evolution for a participant for breakfast with exercise.

The median of 3 new proposed ICRs (ICR_b) was taken with the initial ICR (ICR_a) to calculate a mean average ICR (ICR_c) and this was used to update the case base.

If a participant overrode the insulin dose recommendation, the algorithm was able to use this case for adaptation in certain situations. For example, if a participant took a higher or lower insulin dose than recommended and the postprandial minimum glucose level was in target, the submission could be used in the and the new proposed ICR would be more or less aggressive respectively. Also, if a participant took less insulin than recommended and their minimum glucose was still low, the submission could be accepted and the new proposed ICR would be less aggressive. Similarly, if a participant took more insulin than recommended and the minimum glucose was still high, the submission could be accepted and the new proposed ICR would be more aggressive.

Submissions were rejected automatically from inclusion in the case base if they met certain criteria. Exclusion criteria were as follows:

- ≤ 10g (classed as a snack)

- eating another meal < 1 hour before or 1-4 hours after a meal submission (unless the blood glucose was <4.5 mmol/l in the 2-6 hour postprandial window prior to the second submission, in which case the first submission would be accepted and the new proposed ICR for the first submission would be less aggressive)
- correction doses given pre or post meal (unless postprandial correction dose taken <3 hours after the submission and minimum glucose level in target, in which case new proposed ICR would be more aggressive)
- late advice (>15 minutes after the meal)
- dual bolus
- missing CGM data (>1 hour)
- pre-menstrual cycle adjustment
- illness

2.7 Additional study components

Throughout the study, all participants used the Dexcom G6 RT-CGM system and the Fitbit Charge 3 watch as an activity tracker. An overview of the technology components is shown in Figure 2.7 below.



Figure 2.7: ABC4D system overview A) Participants wear the Dexcom G6 sensor, a Fitbit Charge 3 watch and use an iPhone to display the ABC4D application. B) The ABC4D clinical web portal.

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Chapter 3: Study Objectives & Methodology

3.1 Hypothesis, Aims and Objectives & Regulatory Approvals

3.1.1 Hypothesis

The ABC4D is non-inferior to a standard bolus calculator in adults with T1D on MDI and does not lead to a clinically significant difference in the percentage of time spent in target blood glucose range (3.9-10mmol/L; 70-180 mg/dL).

3.1.2 Aims and Objectives

The study objective was to determine the safety and efficacy of the ABC4D compared to a standard bolus calculator in adults with T1D on MDI in an out of clinic setting.

3.1.3 Regulatory Approvals

The following approvals were obtained:

London-Chelsea Research Ethics Committee (REC): REC reference 13/LO/0264

Imperial College Research Governance & Integrity team (Research Sponsor) and Imperial College Healthcare NHS Trust: Reference number 15SM2847

Medicines & Healthcare Products Regulatory Agency (MHRA): CI/2013/0006

The study (phase 5) has been registered with clinicaltrials.gov: NCT03963219).

3.2 Study design

This was a single-site prospective randomised controlled non-inferiority crossover study. Following a 2-week run in phase, participants were randomised to intervention (ABC4D) arm or control (non-adaptive bolus calculator) arm for the first 12 weeks. Participants were blinded to their treatment group allocation. Participants then underwent a 6-week washout period and were crossed over to the other arm for the final 12 weeks (Figure 3.1). The study duration for each participant was 32 weeks.

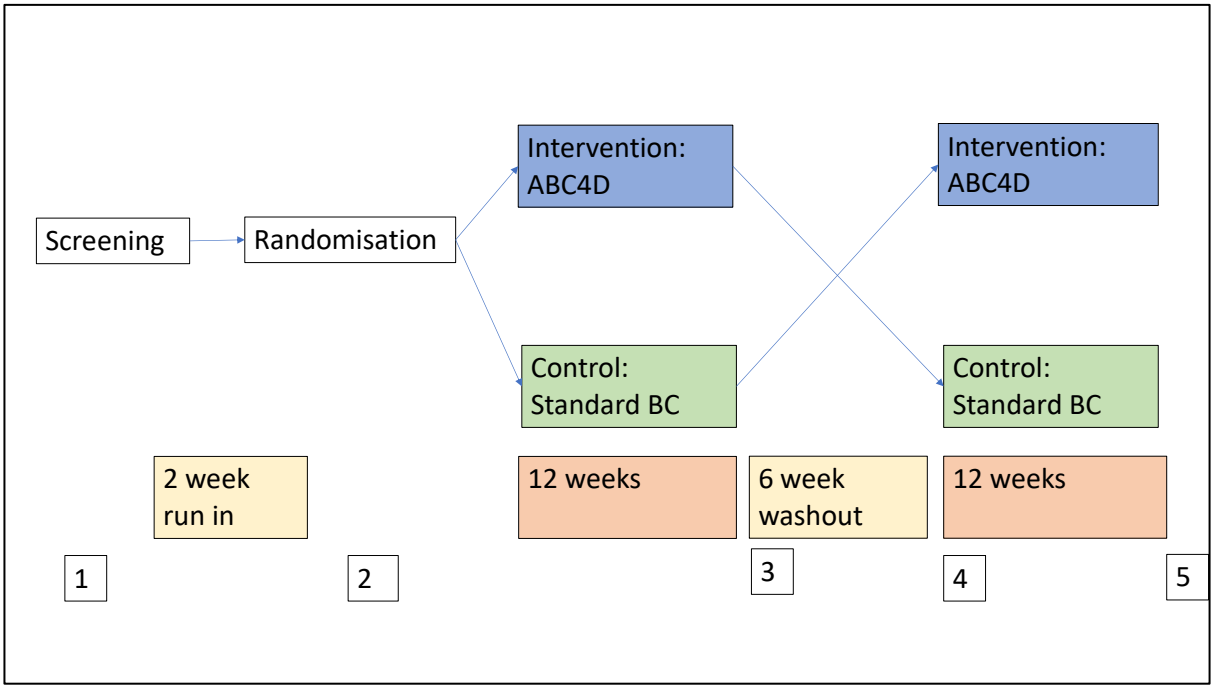


Figure 3.1: Study design

Abbreviations: Advanced Bolus Calculator for Type 1 Diabetes (ABC4D); Bolus calculator (BC)

3.3 Participants and recruitment

3.3.1 Eligibility criteria

Participants were recruited in accordance with the following eligibility criteria:

Inclusion Criteria:

- Adults over 18 years of age
- HbA1c ≥7.0% and ≤ 9.0% (53 mmol/mol to 75 mmol/mol)
- Type 1 diabetes confirmed on the basis of clinical features and a fasting c-peptide <200 pmol/L (C-peptide not required if remote recruitment)
- Type 1 diabetes for greater than 3 years
- On an intensified multiple dose insulin injection regimen for > 6 months (MDI)
- Structured education (either group or 1:1)

Exclusion criteria:

- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Severe visual impairment
- Reduced manual dexterity
- Unable to participate due to other factors, as assessed by the Chief Investigator
- Shift worker
- Allergy or intolerance to insulin aspart
- Known Ischaemic Heart Disease (for remote recruitment)

- History of renal impairment or uncontrolled thyroid disease (for remote recruitment)

3.3.2 Recruitment

Participants were recruited from diabetes clinics at Imperial College Healthcare NHS Trust, attendance lists from structured education (Dose Adjusted for Normal Eating) courses at Imperial College Healthcare NHS Trust, the Imperial College diabetes technology research group database and from interested participants who had contacted the research team. Invitation was by email or telephone contact. Participants were sent the Participant Information Sheet (PIS) and invited to attend a screening visit after at least 48 hours had elapsed, either face to face at the Imperial Clinical Research Facility at Hammersmith Hospital or a remote screening visit during the Covid-19 pandemic.

3.4 Study visits

Following the start of the Covid-19 pandemic, a non-substantial amendment permitted remote study visits in place of face to face study visits for participants already recruited and active recruitment was paused. Recruitment was conducted face to face August 2019 and March 2020 and then remotely for the remaining participants between October 2020 and February 2021, following a substantial amendment. Remote visits were conducted over the telephone or video call. Table 3.1 summarises the study visits.

Activity / Visit no	Study visit 1	Study visit 2	Study visit 3	Study visit 4	Study visit 5	Additional information
Consent	x					
Medical history taking	x					
Urinary pregnancy test (for women of child bearing age)	x					By post if remote recruitment
Urinary albumin:creatinine	x					Not done if remote recruitment
Venous bloods for glucose, c-peptide, thyroid function tests, renal function)	x					Not done if remote recruitment
Insertion of CGM sensor	x					Participants changed the sensor every 10 days at home throughout the study
Study Questionnaire/s	x		x		x	By email/post if remote visit
HbA1c	x		x	x	x	By post if remote visits or HbA1c undertaken for standard clinical practice accepted if within 2 weeks of the study visit.
Weight	x		x		x	Asked participant if recent weight available for remote visits
CGM review with participant		x		x		
Randomisation + initialise the intervention/control		x		x		Randomisation done at visit 2, crossed over at visit 4
Telephone consultation 1 month after study visit		x		x		

Table 3.1: Study Visits

Abbreviations: Continuous glucose monitoring (CGM)

Visit 1 (screening visit)

Following confirmation of eligibility, informed written consent was obtained. Participants recruited remotely were contacted by telephone to discuss the study and then returned their signed consent form by post. The research team then counter-signed the consent form and

emailed or posted a copy of the fully signed consent form to the participant. A full medical and medication history was obtained and a semi-structured interview was undertaken. This included collecting demographic information such as year of diagnosis, length of time on intensified MDI regime, basal insulin type and dose and bolus insulin type, history of severe hypoglycaemia episodes, smoking status and average number of alcohol units consumed per week, retinopathy and nephropathy status, occupation, whether they drive and exercise type and frequency. Participants were also asked about their recent blood glucose values, their current insulin to carbohydrate ratios and insulin sensitivity factor, average grams of carbohydrate consumed per day and details regarding the structured education they had received. Participants completed the following validated study questionnaires: Diabetes Quality of Life (DQOL), Diabetes Treatment Satisfaction questionnaire (DTSQ), Problem Areas in Diabetes (PAID) and Gold score (Table 3.2).

Face to face recruitment: venous blood samples (HbA1c, renal function, plasma glucose, serum c-peptide and thyroid function tests) and urine samples were obtained (albumin: creatinine and urinary pregnancy test for women of child bearing age). An electrocardiogram (ECG) and height, weight and blood pressure measurements were undertaken.

Remote recruitment: Participants returned a postal fingerprick HbA1c sample to the laboratory. This was not required if participants had a laboratory HbA1c result within the last 3 months which met the inclusion criteria. Participants' most recent relevant bloods were accessed by the clinical research team. Venous blood samples, urinary albumin: creatinine ratio and an ECG were not required for remote recruitment. Women of childbearing age undertook a home

urinary pregnancy test. Participants self-reported their height and most recent weight measurement.

For both face to face and remote recruitment

Participants used their own iPhones or were provided with a study iPhone if required. Participants commenced a 2-week run in phase using the Dexcom G6 RT-CGM with standardised education provided as per manufacturer's guidance. Participants were instructed to change the sensor every 10 days or earlier in case of sensor failure. Participants were advised to perform a confirmatory fingerprick blood glucose in the following situations; there was not both a sensor glucose number and arrow representing the glucose rate of change displayed, their symptoms did not match the RT-CGM glucose readings, transmitter or sensor failure or the sensor glucose was out of the measured range (2.2 - 22.2 mmol/L).

Guidance was provided for driving as per the Driver and Vehicle and Licensing Agency (DVLA) advice for using RT-CGM in insulin-treated diabetes (225). Alarms were standardised as follows: high alert at 13.8 mmol/L (250mg/dL), urgent low at 3.1 mmol/L (<56 mg/dL), urgent low soon (predictive hypoglycaemia alert) on. Participants could add an additional low alert and change alert settings later if they wished. A Fitbit Charge 3 watch was set up for participants and training provided.

Participants were initially switched to a Bluetooth insulin pen for their bolus insulin and used an insulin cap device to log basal insulin doses: there were both subsequently removed from the study due to technical issues and following participant feedback. Participants were switched

to an alternative half unit bolus insulin pen and asked to log changes to basal insulin doses in the ABC4D app or Dexcom G6 app during the run in and washout phases. Participants continued their usual bolus and basal insulin throughout the study with the exception of those using Fiasp (insulin aspart) who were switched to Novorapid (insulin aspart) for the study duration.

Visit 2

The run in CGM data was reviewed. The basal dose was not optimised; it was only changed if there were safety issues i.e. problematic hypoglycaemia. Participants were asked to keep their basal dose the same throughout the study unless there were safety issues. A structured education refresher on carbohydrate counting and hypoglycaemia management was provided from a pre-defined curriculum supported by independent written materials, which were posted or emailed to participants in advance of remote study visits.

Participants were randomised to the ABC4D or standard bolus calculator using sealedenvelope.com and stratified by HbA1c (>64 mmol/mol; 8%). The ABC4D app was set up on participants' own iPhones or study iPhones and training was provided, supported by a written user guide. Participants were advised to override the recommended dose if they did not agree with it and enter the dose they wished to take instead.

Participants had a telephone consultation with the research team at 1 month to manage any technology issues. I reviewed data on the clinicians' platform every 2 weeks with no routine insulin adjustments and no changes to ICRs made. If I identified any safety issues, these were

discussed with the research team and participant and therapeutic changes recommended if deemed necessary for safety reasons (for example reduction in basal insulin if recurrent nocturnal hypoglycaemia).

Visit 3

Participants took part in a semi-structured interview which included questions regarding participants' general health, changes to basal insulin dose or any other medication and their experiences of using the ABC4D app, Fitbit and Dexcom G6. Participants completed the following validated questionnaires; DQOL, DTSQ, Gold score, PAID (Table 3.2). Participants also completed the unvalidated ABC4D acceptability questionnaire. A HbA1c sample was obtained.

During the washout period, participants reverted to usual care, calculating bolus insulin doses using the same method as prior to recruitment (manually or standard bolus calculator). Participants continued to use the Dexcom G6 and Fitbit Charge 3 watch during the washout period.

Visit 4

The last 2 weeks of CGM data was reviewed and changes to the basal dose only made if safety issues i.e. problematic hypoglycaemia, with advice to keep their basal dose the same throughout the second treatment phase unless there were safety issues. Participants' current settings (ICR/ISF) and meal timings were confirmed. Participants were crossed over to the other arm for 12 weeks and ABC4D app refresher training was provided. A HbA1c sample was

obtained. Participants had a telephone consultation with the research team after 1 month to manage any issues with the technology.

Visit 5

Participants underwent a semi-structured interview with the same information collected as at visit three and completed the following validated study questionnaires; DQOL, DTSQ, Gold score, PAID (Table 3.2). Participants also completed the ABC4D acceptability questionnaire. A HbA1c sample was obtained. Fitbit and Dexcom Clarity data were synced and downloaded. Participants logged out of or deleted study apps and returned study equipment by post.

Amendments to facilitate remote study visits

Study equipment and questionnaires were sent by post or email in advance prior to remote study visits. HbA1c results were processed from venous laboratory samples for face to face visits and postal fingerprick samples for remote visits, following the substantial amendment. Requests for postal HbA1c samples were sent to the laboratory in advance of remote study visits. Participants were emailed an instructional video and undertook a fingerprick blood sample for HbA1c and posted it back to the laboratory for analysis. Alternatively, a HbA1c taken for standard clinical practice within the 2 week window around a study visit was deemed acceptable for remote visits.

	Description	Interpretation of scores
Diabetes Treatment Satisfaction Questionnaire Status version (DTSQ (S)) (226)	8 item measure: Each item is scored from 0 to 6 "Total score" is the sum of 6 of these items (items 1,4,5,6,7,8) (out of 36) 2 items are scored individually: Perceived fear of hyperglycaemia (item 2) and hypoglycaemia (item 3)	Higher scores indicate greater treatment level satisfaction (0 represents very dissatisfied and 36 represents very satisfied) Perceived fear of hyperglycaemia and hypoglycaemic scored from 0 "none of the time" to 6 "most of the time".
Problem Areas in Diabetes (PAID) (227)	20 item measure: Each item scored on a 5 point Likert scale from 0 to 4 The summation of scores is multiplied by 1.25 to give a total score out of 100.	Scored from 0 (not a problem) to 4 (serious problem) Higher scores indicate greater diabetes related emotional distress
Diabetes quality of life (DQOL) (228)	46 core items categorised into 4 primary scales. 1) Satisfaction (15 items) 2) Impact (20 items) 3) Diabetes worry (4 items 4) Social/vocational worry (7 items) Each item is scored on a 5 point Likert scale.	Satisfaction scored from 1 (very satisfied) to 5 (very dissatisfied) Impact and worry scored from 1 (no impact or never worried) to 5 (always impacted or always worried) Scored as proposed by Jacobson et al (229, 230): a) Responses are reversed scored except impact items 8 and 16 b) The raw scale score is then translated into a 100 point scale* where 1= lowest possible QOL and 100=highest possible QOL, adjusting for items missed or marked as not applicable c) Results from subscales included if participants complete n items in each subscale (230) ≥ 12 items satisfaction subscale ≥ 16 items impact subscale ≥ 2 items diabetes-related worry ≥ 5 items social / vocational worry
GOLD score (164)	Awareness of hypoglycaemia scored on a visual analogue scale of 1 to 7	1 (always aware of the onset of hypoglycaemia) to 7 (never aware of the onset of hypoglycaemia) Scores of ≥ 4 indicate impaired hypoglycaemia awareness

Table 3.2: Description and Interpretation of Scores for Validated Study Questionnaires

* Transformed scale = ((raw score – lowest possible score)/raw score range) X 100 (229) (formula derived from that used for scoring the Medical Outcome Study Health Survey 36 item short form (SF36) questionnaire (231))

Raw score range = highest possible score-lowest possible score (229)

If a subject misses or marks an item as not applicable, then the lowest possible score and raw score range is based on the actual number of items answered for that section on the 1 to 5 scale. (229)

3.5 Study outcomes

Primary outcome:

The difference in percentage time spent in target range (3.9-10mmol/L; 70-180 mg/dL) between intervention (ABC4D) and control (non-adaptive bolus calculator arm) during the daytime (07:00-22:00). This daytime period was chosen as it was expected that most participants would use the bolus calculator for meals within this timeframe.

Secondary outcomes:

- Percentage of time spent below range (< 3.0 mmol/L: < 54 mg/dL), (< 3.9 mmol/L; < 70 mg/dL)]
- Percentage of time spent in euglycaemia (3.9-7.8 mmol/L; 70-140 mg/dL)
- Percentage of time spent above range (>10mmol/L; > 180 mg/dL)
- Percentage time spent in target range (3.9-10mmol/L; 70-180 mg/dL) during the night and over a 24-hour period.
- Number of hypoglycaemic events (defined as consecutive glucose readings <3.0mmol/L (<70 mg/dL) for ≥ 20 minutes separated by ≥ 30 minutes of consecutive glucose readings ≥3.0 mmol/L between events)
- Glycaemic variability (evaluated glycaemic variability measures were co-efficient of variation (CV), standard deviation (SD), low blood glucose index (LBGI) and mean absolute glucose change per unit time (MAG))

- Change in HbA1c
- Frequency of severe hypoglycaemia episodes requiring third party assistance.
- Psychology outcome scores from validated questionnaires (PAID, DTSQ, DQOL)
- Usability of the ABC4D app and continuous glucose monitoring obtained through questionnaires.

3.6 Statistical Analysis

The following statistical tests were undertaken to assess the differences at baseline between the control first and intervention first groups; for categorical variables the Wilcoxon sum rank test was used and for quantitative variables the Pearson Chi-squared test was used when the expected frequency in each cell was at least 5, otherwise the Fisher's exact test was used. Participants were required to have fully completed the study (both control and intervention phases) and have at least 70% CGM data in both the control and intervention phases as per consensus recommendations (65) in order to be included in the analysis. Glucose data were exported from Dexcom Clarity. Easy GV (v10.0) software (232) was used to calculate measures of glycaemic variability. Glucose management indicator (GMI) values were obtained from Dexcom Clarity or if not available, calculated from mean glucose (233, 234) for the relevant period derived in Easy GV.

Baseline glucose outcomes were analysed to compare the 2 week RT-CGM period prior to each treatment period to the last 2 weeks of each treatment period. The reason for choosing the last 2 weeks of the treatment periods was to allow the adaptive bolus calculator enough time to have adapted the ICRs and therefore evaluation of the impact on glycaemic outcomes.

Glucose data on study visit days was excluded from the analysis. The Wilcoxon Signed rank test was used to assess between and within group differences. The analyses of primary and secondary CGM outcomes were performed separately for daytime (0700-2200), night-time (2200-0700) and 24 hours. A post hoc analysis was undertaken for participants with an average of ≥3 meal submissions/day across the ABC4D and control periods to investigate change in glycaemic outcomes during the daytime (07:00-22:00) and 24 hour period. An additional post hoc sub-analysis evaluated the change in glycaemic outcomes during the daytime for participants with at least 90% acceptance of all submissions (meal, snacks and correction doses) during both the control and intervention phases. A pairwise analysis used the Wilcoxon rank sum test to compare the change in glycaemic outcomes between baseline users of RT-CGM/ intermittently scanned CGM (isCGM) and those of SMBG, performed separately for the control and intervention periods.

The following co-variates were used in multivariable linear regression analysis of variation in %TIR change during the intervention period: duration of diabetes, age, gender, baseline 2 weeks %TIR (3.9-10.0mmol/L; 70-180mg/dL), baseline RT-CGM/isCGM use and percentage of submissions accepted by the algorithm. Data from the ABC4D clinical web platform were exported and ABC4D outcomes were investigated in post-hoc analyses. Between group differences were assessed using the Wilcoxon signed rank test. Scatter graphs were used to examine the correlation between the average number of app meal uses/week for the last 2 weeks or entire control/intervention periods and change in daytime glycaemic outcomes. Linear regression was undertaken for cases in which visual inspection of the scatter graph suggested a possible correlation. Graphs were generated in Microsoft Excel version 16.66.1 (Microsoft Corporation, Washington, US) to display participants' responses to aggregated ABC4D acceptability questions.

Statistical analysis was performed using Stata/BE version 17.0 (StataCorp, Texas). Data are presented as median (interquartile ranges) unless otherwise stated. All tests were two tailed with $p<0.05$ considered statistically significant.

Power Calculation:

Pilot data expects %TIR 3.9-10.0 mmol/L (70-180 mg/dL) after treatment with a standard bolus calculator to be 63 % (unpublished data), with a standard deviation of 9.4% difference between treatment groups. A poorer outcome of up to 5% difference in %TIR with ABC4D compared to a standard bolus calculator would be considered to be clinically insignificant and equivalent/non-inferior. With 90% power and alpha 0.05, 32 participants would need to be recruited. We aimed to recruit 37 participants to allow for a drop out rate of 15%.

Chapter 4: Results

The main results in this chapter have been accepted for publication in Diabetes Technology and Therapeutics (219). An abstract evaluating case parameter use and selected ABC4D acceptability questionnaire results at the end of the study has been accepted for poster presentation at the Advanced Technologies and Treatments for Diabetes conference 22nd-25th February 2023 in Berlin.

4.1 Baseline Demographics

Figure 4.1 summarises recruitment. I screened 43 participants of whom 7 were excluded. Four participants did not meet the inclusion criteria; HbA1c too low (n=2) and HbA1c too high (n=2), including one participant who was later re-screened and met the eligibility criteria. A further 3 participants were excluded for other reasons; following a low carbohydrate diet (n=1), nickel allergy (n=1), finds technology challenging (n=1). Thirty-seven participants were randomised. Participants were 57% male, aged (median (IQR)) 44.7 (28.2-55.2) years old and with a duration of T1D of 15.0 (9.5-29.0) years (Table 4.1). There were three (8.1%) users of RT-CGM and 15 users of isCGM (40.5%) at baseline. There were no statistical differences between the control first and intervention first groups at baseline.

The following basal insulins were used at baseline: insulin detemir (n=21 (56.8%)), glargine (n=12 (32.4%)) and degludec (n=4 (10.8%)). The following bolus insulins were used at baseline: Novorapid (insulin aspart) (n=27 (73.0%)), Humalog (insulin lispro) (n=7 (18.9%)) and Fiasp (insulin aspart) (n=3 (8.1%)). Those participants using Fiasp (n=3) were switched to

Novorapid for the duration of the study. One participant experienced persisting hypoglycaemia during the run-in period despite a reduction in twice daily insulin glargine doses and therefore was switched to twice daily insulin detemir at randomisation, in line with routine clinical practice.

Data were analysed from 33 participants (Figure 4.1). Three participants were withdrawn during the study; one participant experienced ongoing skin reactions to the Dexcom sensor dressing, one participant wished to return to their usual Fiasp insulin (insulin aspart) and one participant was deliberately omitting insulin doses. The data from one participant was excluded from the analysis as they used the ABC4D app incorrectly for the first intervention phase and entered carbohydrate amounts into the ABC4D app when they wished to take a correction dose only and therefore these were incorrectly logged as meal or snack submissions.

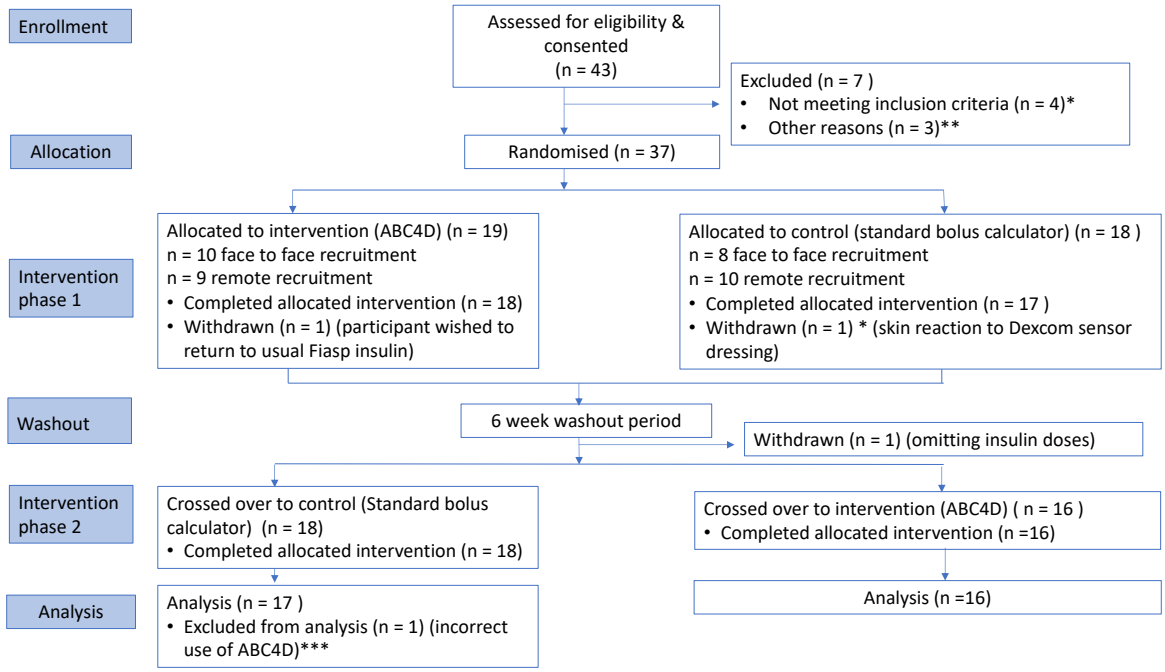


Figure 4.1: Consort flow diagram

Reproduced with permission from Unsworth et al (219) (with text enlarged and minor adjustments to the figure to accommodate this)

*HbA1c too high (n = 2) including one participant who was later re-screened and met eligibility criteria, HbA1c too low (n = 2).

** Other reasons for exclusion: participant following a low carbohydrate diet (n = 1), nickel allergy (n = 1), finds technology challenging (n = 1)

*** Incorrect use of ABC4D: participant entered carbohydrate amounts into the bolus calculator application when wished to take a correction dose only and not consume any food. These submissions were incorrectly logged as snacks/meals for the first intervention phase.

	Total n = 37	Control first n = 18	Intervention first n = 19	P value control first vs intervention first
Gender (male)	21 (56.8)	11 (61.1)	10 (52.6)	0.60
Age (years)	44.7 (28.2- 55.2)	37.8 (27.2-56.4)	48.0 (30.7-55.2)	0.41
Duration of type 1 diabetes (years)	15.0 (9.5- 29.0)	14.0 (9.5-16.0)	17.0 (7.0-36.0)	0.47
BMI (kg/m2)	25.2 (22.5- 28.2)	24.6 (22.5-29.2)	25.3 (22.5-28.2)	0.83
Ethnicity: Caucasian Asian Black Caribbean Chinese Mixed race	 32 (86.5) 2 (5.4) 1 (2.7) 1 (2.7) 1 (2.7)	 16 (88.9) 1 (5.6) 0 1 (5.6) 0	 16 (84.2) 1 (5.3) 1 (5.3) 0 1 (5.3)	1.00
Smoking status: Never smoked Ex-smoker Current smoker	 24 (64.9) 9 (24.3) 4 (10.8)	 9 (50.0) 5 (27.8) 4 (22.2)	 15 (79.0) 4 (21.1) 0	0.057
Alcohol units per week	9.0 (3.0-17.0)	8.5 (1.7-14.0)	12.0 (3.5-18.0)	0.27
Previous episode of severe hypoglycaemia	17 (47.2)	8 (44.4)	9 (50.0)	0.74
Diabetic retinopathy and maculopathy: R0/R1 R2 R3 M0 M1	 35 (94.6) 0 2 (5.4) 33 (89.2) 4 (10.8)	 17 (94.4) 0 1 (5.6) 15 (83.3) 3 (16.7)	 18 (94.7) 0 1 (5.3) 18 (94.7) 1 (5.3)	 1.00* 0.34**
Hypoglycaemia awareness (GOLD score <4)	34 (91.9)	16 (89.9)	18 (94.7)	0.60
Baseline user of RT-CGM	3 (8.1)	2 (11.1)	1 (5.3)	0.60
Baseline user of isCGM	15 (40.5)	7 (38.9)	8 (42.1)	0.84
History of microalbuminuria	4 (10.8)	1 (5.6)	3 (15.8)	0.60
Baseline HbA1c (mmol/mol) Baseline HbA1c (%)	61.0 (58.0 -67.0) 7.7 (7.5- 8.3)	63.5 (59.0-72.0) 8.0 (7.5-8.7)	59.0 (55.0-66.0) 7.5 (7.2- 8.2)	0.08
Total daily basal insulin dose	24 (17-35)	23 (13-42)	28 (18-30)	0.84

Table 4.1: Baseline Demographic information for participants randomised and differences between the control first and intervention first groups Reproduced with permission from Unsworth et al (219)

Results presented as n (%) or median (IQR).

* p value for differences in retinopathy screening ** p value for differences in maculopathy staging

Abbreviations: RT-CGM (real time continuous glucose monitoring)**;** isCGM (intermittently scanned continuous glucose monitoring).

4.2 Glycaemic Outcomes

4.2.1 Time in range

For the primary outcome of percentage time in range (TIR) 3.9-10.0 mmol/L (70-180mg/dL) change during the daytime (07:00-22:00), there was no difference between ABC4D and control (median (IQR) change +0.1 (-2.6 to + 4.0)% versus +1.9 (-3.8 to + 10.1)% (p = 0.53) (Table 4.2). There was also no difference in percentage TIR change between ABC4D and control during the night-time (22:00-07:00) (1.9 (-5.4 to 11.7)% versus 2.6 (-8.2 to 8.5)% (p = 0.98)) (Table 4.3) or during the 24 hour period (1.2 (-4.1 to 4.7)% versus 2.8 (-3.4 to 8.2)%; p =0.66) (Table 4.4).

There were no within group significant percentage TIR changes between the last 2 weeks of intervention/control and the pre-intervention/control periods respectively during the daytime (Table 4.2), night-time (Table 4.3) or 24 hour period (Table 4.4).

4.2.2 Time below range

There were no significant differences in percentage time below range (TBR) change at various thresholds (<3.9 mmol/L; <70mg/dL), (<3.0 mmol/L; <54 mg/dL), (<2.8 mmol/L; <50mg/dL) between ABC4D and control during the daytime (Table 4.2), night-time (Table 4.3) or 24 hour period (Table 4.4). The percentage TBR <3.0 mmol/L change during the daytime was 0.0 (-0.2 to 0.1)% with ABC4D compared to -0.1 (-0.3 to 0.0)% with control, p = 0.84 (Table 4.2).

A within group difference was observed between the 2 weeks pre-control compared to the last 2 weeks of the control during the daytime for percentage TBR <3.0 mmol/L (0.3 (0.0-0.6)%) pre-control versus 0.1 (0.0-0.3)% last 2 weeks; p = 0.04) and percentage TBR <2.8 mmol/L (0.2 (0.0-0.4)% versus 0.0 (0.0-0.1)%; p=0.01) (Table 4.2). This difference was also observed during the 24 hour period for the control group for percentage TBR <3.0 mmol/L (0.3 (0.0-0.7)% pre-control versus 0.2 (0.1-0.4)% last 2 weeks; p=0.02) and percentage TBR <2.8 mmol/L (0.2 (0.0-0.5) versus 0.1 (0.0-0.2)%; p = 0.03) (Table 4.4). This within group difference for the control group was not observed for the night-time period (Table 4.3). There were no within group differences in percentage TBR at any threshold observed for ABC4D during the daytime (Table 4.2), night-time (Table 4.3) or 24 hour period (Table 4.4).

4.2.3 Time above range

There were no differences observed in percentage time above range (TAR) change between the ABC4D and control during the daytime at the threshold of >10.0 mmol/L (-0.8 (-3.4 to 3.0) versus -2.8 (-9.9 to 5.3); p = 0.49) or >13.9 mmol/L (0.5 (-1.8 to 3.5) versus -0.2 (-8.4 to 3.6); p =0.28) (Table 4.2). There were also no differences found in percentage TAR >10.0 mmol/L or >13.9 mmol/L change between ABC4D and control during the 24 hour period (Table 4.4) or night-time period (Table 4.3).

There were no within group differences found for percentage TAR >10.0 mmol/L or >13.9 mmol/L during the last 2 weeks of intervention/control compared to pre intervention/control respectively for the daytime (Table 4.2), night-time (Table 4.3) or 24 hour period (Table 4.4).

4.2.4 Glycaemic variability measures

No differences were observed in change in glycaemic variability measures (mean, standard deviation (SD), co-efficient of variation (CV), low blood glucose index (LBGI) or mean amplitude of glucose (MAG)) between ABC4D and control during the daytime (Table 4.2), night-time (Table 4.3) or 24 hour period (Table 4.4). There were no within group differences for ABC4D or control in the aforementioned glycaemic variability measures during the daytime (Table 4.2), night-time (Table 4.3) or 24 hour period (Table 4.4).

	Pre-control	Last 2 weeks of control	Change control	P value last 2 weeks of control vs pre control	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value last 2 weeks of intervention vs pre-intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	49.4 (42.1-61.1)	52.3 (43.4-63.0)	1.9 (-3.8 to 10.1)	0.18	51.2 (45.1-59.9)	50.5 (47.2-58.0)	0.1 (-2.6 to 4.0)	0.59	0.53
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	28.4 (19.0-39.2)	27.7 (19.6-39.0)	0.5 (-7.4 to 6.7)	0.84	28.7 (22.4-36.0)	28.3 (23.9-32.9)	2.2 (-5.7 to 5.0)	0.99	0.73
% TBR < 3.9 mmol/L (<70 mg/dL)	1.6 (0.5-3.4)	1.4 (0.3-3.1)	-0.1 (-1.1 to 0.5)	0.47	1.2 (0.5-3.0)	1.4 (1.0-2.5)	-0.1 (-0.7 to 0.6)	0.53	0.85
% TBR < 3.0 mmol/L (<54 mg/dL)	0.3 (0.0-0.6)	0.1 (0.0-0.3)	-0.1 (-0.3 to 0.0)	**0.04**	0.2 (0.0-0.5)	0.2 (0.1-0.6)	0.0 (-0.2 to 0.1)	0.24	0.84
% TBR < 2.8 mmol/L (<50 mg/dL)	0.2 (0.0-0.4)	0.0 (0.0-0.1)	-0.1 (-0.4 to 0.0)	**0.01**	0.1 (0.0-0.4)	0.1 (0.0-0.3)	-0.1 (-0.2 to 0.0)	0.05	0.93
% TAR >10 mmol/L (> 180 mg/dL)	47.8 (34.3-56.6)	44.8 (33.3-54.1)	-2.8 (-9.9 to 5.3)	0.31	43.5 (35.5-51.7)	47.4 (38.2-50.7)	-0.8 (-3.4 to 3.0)	0.70	0.49
% TAR > 13.9 mmol/L (>250 mg/dL)	15.6 (5.6 -20.6)	12.6 (6.5-16.8)	-0.2 (-8.4 to 3.6)	0.32	13.5 (6.9-19.6)	14.8 (9.4- 19.7)	0.5 (-1.8 to 3.5)	0.26	0.28
Mean	10.1 (8.7-11.0)	9.5 (8.9-10.6)	-0.5 (-0.8 to 0.7)	0.49	9.8 (9.0-10.4)	10.0 (9.3-10.5)	0.1 (-0.5 to 0.5)	0.50	0.26
SD	3.4 (3.1-3.7)	3.3 (3.0-3.7)	-0.1 (-0.4 to 0.2)	0.39	3.4 (3.0-3.8)	3.4 (3.2-3.9)	0.1 (0.0 to 0.2)	0.13	0.08
CV	34.1 (32.1-38.3)	33.6 (31.1-37.4)	-0.3 (-2.6 to 1.3)	0.54	35.6 (31.7-39.2)	34.9 (33.5-37.8)	0.0 (-1.2 to 2.0)	0.70	0.48
LBGI	0.5 (0.2-1.0)	0.4 (0.2-0.8)	0.0 (-0.4 to 0.2)	0.56	0.4 (0.3.-0.8)	0.5 (0.3-0.7)	0.0 (-0.2 to 0.1)	0.35	0.65
MAG	3.4 (3.1-3.6)	3.5 (3.1-3.7)	0.0 (-0.3 to 0.3)	0.57	3.4 (2.9-3.8)	3.3 (3.1-3.8)	0.1 (-0.2 to 0.2)	0.50	0.94

Table 4.2: Glycaemic outcomes for **daytime (07:00-22:00)** for the control and intervention periods (n =33).

All values median (IQR).

Adapted with permission from Unsworth et al (219), with the addition of statistical within group differences between the last 2 weeks of the intervention/control compared to pre-intervention/control.

	Pre-control	Last 2 weeks of control	Change control	P value last 2 weeks of control vs pre control	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value last 2 weeks of intervention vs pre-intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	47.5 (36.8 – 62.3)	51.3 (36.1-60.2)	2.6 (-8.2 to 8.5)	0.69	47.9 (35.6 – 59.0)	49.2 (31.2-60.2)	1.9 (-5.4 to 11.7)	0.62	0.98
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	27.8 (17.1- 37.5)	30.4 (19.6- 39.1)	1.5 (-8.9 to 9.2)	0.66	28.7 (19.9-33.3)	27.8 (17.3-37.5)	2.6 (-3.4 to 6.1)	0.43	0.71
% TBR < 3.9 mmol/L (<70 mg/dL)	1.6 (0.5- 3.9)	1.5 (0.1-2.7)	-0.3 (-1.8 to 1.0)	0.33	1.2 (0.2-2.0)	1.3 (0.6-3.3)	0.2 (-0.4 to 1.0)	0.21	0.16
% TBR < 3.0 mmol/L (<54 mg/dL)	0.1 (0.0-0.8)	0.0 (0.0 -0.5)	0.0 (-0.3 to 0.0)	0.29	0.0 (0.0-0.4)	0.1 (0.0-0.3)	0.0 (-0.1 to 0.1)	0.76	0.35
% TBR < 2.8 mmol/L (<50 mg/dL)	0.0 (0.0-0.5)	0.0 (0.0-0.3)	0.0 (-0.2 to 0.0)	0.20	0.0 (0.0-0.1)	0.0 (0.0–0.2)	0.0 (-0.1 to 0.0)	0.92	0.67
% TAR >10 mmol/L (> 180 mg/dL)	48.0 (33.9-59.5)	44.0 (35.3-60.8)	-2.6 (-9.1 to 10.2)	0.81	50.0 (37.4-62.3)	49.9 (34.2-64.9)	-2.0 (-12.4 to 5.6)	0.47	0.80
% TAR > 13.9 mmol/L (>250 mg/dL)	15.5 (6.6-22.7)	13.7 (5.4-30.2)	-1.2 (-5.5 to 7.5)	0.81	12.4 (7.4-27.5)	18.0 (5.2-30.0)	1.8 (-5.2 to 8.6)	0.17	0.33
Mean	10.0 (9.0-11.0)	9.7 (8.9-11.5)	0.0 (-0.9 to 0.8)	0.88	10.2 (9.4-10.8)	10.1 (9.2-11.7)	-0.2 (-0.9 to 0.7)	0.96	0.85
SD	3.5 (3.2-3.9)	3.4 (2.9-3.9)	-0.1 (0.4 to 0.3)	0.59	3.3 (3.1-3.8)	3.6 (3.1-4.0)	0.3 (-0.5 to 0.6)	0.28	0.29
CV	34.8 (31.7-37.6)	34.6 (30.3-39.0)	0.4 (-3.8 to 3.2)	0.82	33.5 (29.4-36.5)	34.2 (31.5-38.6)	-0.2 (-3.3 to 5.2)	0.54	0.35
LBGI	0.5 (0.2-1.0)	0.5 (0.2-0.7)	-0.1 (-0.3 to 0.2)	0.25	0.4 (0.1-0.6)	0.4 (0.2-0.8)	0.1 (-0.1 to 0.2)	0.15	0.15
MAG	2.8 (2.5-3.0)	2.7 (2.4-3.3)	0.0 (-0.1 to 0.4)	0.17	2.6 (2.4-3.1)	2.7 (2.3-3.1)	0.0 (-0.3 to 0.3)	0.87	0.51

Table 4.3: Glycaemic outcomes for **night-time** (22:00-07:00) for the control and intervention periods (n =33).

All values median (IQR).

Adapted with permission from Unsworth et al (219), with the addition of statistical within differences between the last 2 weeks of the intervention/control compared to pre-intervention/control and the addition of international system (SI) units for glucose outcomes

	Pre-control	Last 2 weeks of control	Change control	P value last 2 weeks of control vs pre control	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value last 2 weeks of intervention vs pre-intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	49.8 (41.9 - 62.5)	52.9 (44.5-58.6)	2.8 (-3.4 to 8.2)	0.21	53.0 (40.7 - 57.1)	50.2 (40.1 – 58.3)	1.2 (-4.1 to 4.7)	0.56	0.66
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	28.1 (20.1- 38.9)	31.1 (21.0- 38.8)	1.1 (-4.8 to 7.0)	0.51	29.8 (21.7-33.8)	28.6 (22.5-33.8)	1.5 (-3.3 to 5.6)	0.53	0.61
% TBR < 3.9 mmol/L (<70 mg/dL)	2.2 (0.6-3.0)	1.6 (0.7-3.1)	-0.1 (-1.1 to 0.3)	0.26	1.3 (0.4 -3.1)	1.6 (0.9-2.8)	0.1 (-0.5 to 0.7)	0.75	0.50
% TBR < 3.0 mmol/L (<54 mg/dL)	0.3 (0.0- 0.7)	0.2 (0.1- 0.4)	-0.1 (-0.3 to 0.0)	**0.02**	0.2 (0.1-0.5)	0.2 (0.1-0.5)	0.0 (-0.1 to 0.1)	0.93	0.53
% TBR < 2.8 mmol/L (<50 mg/dL)	0.2 (0.0-0.5)	0.1 (0.0 – 0.2)	-0.1 (- 0.4 to 0.0)	**0.03**	0.1 (0.0-0.3)	0.1 (0.0-0.3)	0.0 (-0.1 to 0.0)	0.34	0.66
% TAR >10 mmol/L (> 180 mg/dL)	45.9 (33.9-55.6)	44.8 (38.6-54.5)	-2.7 (-8.2 to 4.9)	0.36	42.9 (39.2-56.5)	46.2 (39.0 – 56.1)	-0.5 (-5.9 to 5.4)	0.59	0.80
% TAR > 13.9 mmol/L (>250 mg/dL)	14.4 (8.7 – 21.3)	12.9 (7.1-20.5)	-1.4 (-4.6 to 4.8)	0.51	13.8 (8.4 – 23.8)	16.4 (10.5- 22.8)	0.5 (-2.9 to 4.7)	0.23	0.21
Mean	10.0 (8.9-10.9)	9.7 (9.1-10.7)	- 0.3 (-0.5 to 0.7)	0.49	9.7 (9.2-10.8)	9.9 (9.4-10.9)	0.1 (-0.6 to 0.6)	0.66	0.51
SD	3.6 (3.3-3.8)	3.4 (3.1- 3.8)	-0.1 (-0.4 to 0.3)	0.33	3.5 (3.2-3.7)	3.6 (3.3-4.0)	0.1 (-0.2 to 0.5)	0.17	0.08
CV	36.2 (32.6-38.4)	35.5 (31.9-37.1)	-0.4 (-2.8 to 2.7)	0.47	35.0 (31.4-38.2)	35.4 (33.4-38.5)	0.6 (-2.7 to 3.0)	0.30	0.19
LBGI	0.7 (0.2-0.8)	0.5 (0.3-0.8)	0.0 (-0.2 to 0.1)	0.21	0.5 (0.2 – 0.8)	0.5 (0.3 - 0.7)	0.0 (-0.2 to 0.1)	0.85	0.59
MAG	2.8 (2.6-3.1)	2.9 (2.6-3.2)	0.1 (-0.1 to 0.4)	0.09	2.9 (2.5-3.0)	2.9 (2.5 - 3.1)	0.0 (-0.1 to 0.1)	0.60	0.48

Table 4.4: Glycaemic outcomes for the **24-hour period** for the control and intervention periods (n =33).

All values median (IQR).

Adapted with permission from Unsworth et al (219) with the addition of statistical within group differences between the last 2 weeks of the intervention/control compared to pre-intervention/control and the addition of international system (SI) units for glucose outcomes

4.2.5 Post-hoc analyses

Participants with an average of at least 3 meal submissions per day

In a sub-analysis of participants with an average of at least 3 meal submissions per day throughout the intervention and control periods (n=19), there were no differences in change in percentage TIR, TAR or TBR with ABC4D compared to control during the daytime (Table 4.5) or 24 hour period (Table 4.6).

	Pre-control	Last 2 weeks control	Change	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	52.3 (40.9-62.6)	57.5 (47.4-64.2)	6.3 (-3.7 to 10.7)	54.9 (48.6-59.9)	49.8 (47.5-58.0)	-1.0 (-6.4 to 0.7)	0.08
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	27.8 (17.6-39.9)	30.4 (21.3-39.0)	2.4 (-9.6 to 6.7)	29.5 (22.4-36.2)	28.3 (23.6-32.4)	-3.7 (-5.9 to 4.6)	0.38
% TBR < 3.9 mmol/L (<70 mg/dL)	2.2 (0.3-3.6)	1.4 (0.2 – 2.8)	-0.2 (-2.0 to 0.3)	1.2 (0.5- 3.0)	1.6 (1.0-2.5)	-0.1 (-1.6 to 0.8)	0.47
% TBR < 3.0 mmol/L (<54 mg/dL)	0.2 (0.0-0.7)	0.0 (0.0-0.3)	-0.1 (- 0.4 to 0.0)	0.2 (0.0-0.5)	0.1 (0.0-0.4)	0.0 (-0.3 to 0.0)	0.73
% TBR < 2.8 mmol/L (<50 mg/dL)	0.1 (0.0-0.6)	0.0 (0.0-0.1)	-0.1 (-0.4 to 0.0)	0.2 (0.0-0.3)	0.0 (0.0-0.2)	-0.1 (-0.3 to 0.0)	0.75
% TAR >10 mmol/L (> 180 mg/dL)	45.3 (33.3-57.5)	39.7 (32.6-50.8)	-6.7 (-11.8 to 5.3)	42.8 (34.3-50.2)	47.4 (38.2-50.3)	0.4 (-1.7 to 7.9)	0.20
% TAR > 13.9 mmol/L (>250 mg/dL)	10.6 (4.6-22.4)	10.7 (6.5-14.8)	-0.5 (-8.4 to 3.6)	13.5 (8.1-19.1)	14.3 (8.3-20.3)	0.8 (-1.8 to 5.3)	0.18

Table 4.5: Glycaemic outcomes for the daytime period (07:00-22:00) for participants using the app for an average of ≥ 3 meal submissions per day during the control and intervention periods (n = 19)

All values median (IQR).

	Pre-control	Last 2 weeks control	Change	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	50.3 (39.8-63.0)	54.9 (45.6-58.6)	2.8 (-2.7 to 7.3)	54.8 (42.1-57.8)	50.2 (44.5-57.7)	0.8 (-5.6 to 4.0)	0.24
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	28.1 (18.9-38.9)	32.9 (21.0-35.7)	1.1 (-5.5 to 7.0)	31.4 (21.3-34.1)	28.6 (22.8-33.4)	-0.5 (-5.8 to 3.5)	0.38
% TBR < 3.9 mmol/L (<70 mg/dL)	2.3 (0.6-3.4)	1.7 (0.4-3.0)	-0.4 (-1.3 to 0.1)	1.3 (0.9-3.1)	1.9 (0.9-2.6)	0.1 (-0.7 to 0.9)	0.42
% TBR < 3.0 mmol/L (<54 mg/dL)	0.3 (0.0-0.8)	0.2 (0.0-0.3)	-0.1 (-0.6 to 0.0)	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.0 (-0.1 to 0.1)	0.18
% TBR < 2.8 mmol/L (<50 mg/dL)	0.2 (0.0-0.6)	0.0 (0.0-0.2)	-0.1 (-0.5 to 0.0)	0.1 (0.0-0.3)	0.1 (0.0-0.3)	0.0 (-0.2 to 0.0)	0.37
% TAR >10 mmol/L (> 180 mg/dL)	45.3 (33.8-58.8)	42.1 (38.6-51.9)	-3.4 (-7.0 to 5.4)	42.1 (37.9-56.5)	46.2 (39.4-54.0)	0.1 (-5.8 to 5.9)	0.40
% TAR > 13.9 mmol/L (>250 mg/dL)	12.9 (7.0-20.6)	12.6 (7.1-14.0)	-2.3 (-5.2 to 3.1)	12.9 (9.1-17.0)	16.4 (10.6-20.1)	0.4 (-1.7 to 4.7)	0.12

Table 4.6: Glycaemic outcomes for the 24 hour period for participants using the app for an average of ≥ 3 meal submissions per day during the control and intervention periods (n = 19)

All values median (IQR).

Participants who accepted at least 90% of all submissions throughout both the control and intervention phase

A post hoc sub-analysis evaluated change in glycaemic outcomes during the daytime for participants with at least 90 percent acceptance of all submissions (meal, snacks and correction doses) during both the control and intervention phases (n=9). This demonstrated no difference in change in glycaemic outcomes with ABC4D compared to control (Table 4.7).

	Pre-control	Last 2 weeks of control	Change control	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value change intervention vs change control
% TIR 3.9-10 mmol/L (70-180 mg/dL)	49.5 (47.5-56.4)	53.8 (43.4-60.0)	2.2 (-2.5 to 6.3)	48.1 (43.8-54.9)	48.5 (43.0-55.1)	2.2 (-1.9 to 3.3)	0.59
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	30.1 (24.0-35.2)	27.7 (22.9-45.5)	0.5 (-2.0 to 6.9)	29.6 (26.8-35.4)	29.9 (25.4-37.9)	1.0 (-4.9 to 8.3)	0.59
% TBR < 3.9 mmol/L (<70 mg/dL)	3.4 (2.2-4.2)	4.0 (1.4 - 4.4)	-0.2 (-1.3 to 1.0)	4.1 (0.6-6.7)	3.8 (1.7-4.5)	-0.7 (-2.0 to 1.3)	0.77
% TBR < 3.0 mmol/L (<54 mg/dL)	0.6 (0.5-0.9)	0.3 (0.2 - 0.6)	-0.2 (-0.3 to 0.1)	0.7 (0.3-1.4)	0.6 (0.3-1.0)	-0.1 (-0.5 to 0.1)	0.77
% TBR < 2.8 mmol/L (<50 mg/dL)	0.4 (0.2 – 0.7)	0.0 (0.0-0.2)	-0.4 (-0.6 to -0.1)	0.4 (0.1-0.7)	0.3 (0-0.5)	-0.1 (-0.2 to 0.1)	0.72
% TAR >10 mmol/L (> 180 mg/dL)	45.3 (39.2-49.1)	43.3 (33.3-45.4)	-2.8 (-6.7 to 0.9)	43.5 (37.5-54.2)	49.8 (39.9-51.5)	-0.8 (-3.1 to 3.0)	0.37
% TAR > 13.9 mmol/L (>250 mg/dL)	15.6 (11.4-17.4)	8.3 (4.2 -15.4)	-0.1 (-11.3 to 1.9)	14.2 (6.7-19.6)	16.2 (12.5-17.7)	0.8 (-1.7 to 2.0)	0.26

Table 4.7: **Change in glycaemic outcomes during the daytime (07:00-22:00) for participants who accepted ≥90% of submissions (meals, snacks and correction doses) in during both the control and intervention periods** (n=9).

Values presented as median (IQR).

Baseline RT-CGM/isCGM users compared to baseline SMBG users

Pairwise analysis demonstrated no differences in percentage TIR, TAR or TBR change during the daytime between baseline users of RT-CGM/isCGM compared to baseline users of SMBG during the control (Table 4.8) or intervention (Table 4.9) arms.

	Baseline user SMBG (n = 18)			Baseline user RT-CGM or isCGM (n = 15)			P value (RT-CGM/isCGM vs SMBG)
	Pre-control	Last 2 weeks control	Change	Pre-control	Last 2 weeks control	Change	
% TIR 3.9-10 mmol/L (70-180 mg/dL)	51.8 (45.8-68.0)	57.6 (43.4-64.2)	-1.1 (-3.8 to 10.1)	46.2 (37.9-56.4)	47.6 (42.2-59.9)	6.3 (-4.3 to 10.7)	0.37
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	32.6 (24.0-44.7)	31.3 (22.9-41.1)	-0.4 (-9.6 to 6.2)	23.5 (15.7-28.6)	22.0 (17.6-37.8)	4.2 (-4.8 to 9.0)	0.23
% TBR < 3.9 mmol/L (<70 mg/dL)	2.8 (1.0-4.2)	2.0 (1.3-3.1)	-0.2 (-2.1 to 0.9)	0.8 (0.2-2.3)	0.6 (0.2 -2.8)	0.0 (-0.6 to 0.4)	0.77
% TBR < 3.0 mmol/L (<54 mg/dL)	0.3 (0.2-0.9)	0.3 (0.1-0.4)	0.0 (-0.5 to 0.1)	0.2 (0.0 – 0.5)	0.0 (0.0-0.2)	-0.2 (-0.3 to 0.0)	0.65
% TBR < 2.8 mmol/L (<50 mg/dL)	0.2 (0.0-0.6)	0.1 (0.0-0.2)	-0.1 (-0.6 to .0)	0.1 (0.0-0.3)	0.0 (0.0-0.1)	0.0 (-0.2 to 0.0)	0.66
% TAR >10 mmol/L (> 180 mg/dL)	43.4 (28.2-51.4)	39.0 (32.6-47.8)	0.7 (-9.7 to 5.9)	50.1 (42.1-60.9)	49.7 (36.4-55.7)	-6.7 (-10.8 to 4.8)	0.47
% TAR > 13.9 mmol/L (>250 mg/dL)	13.1 (4.6-20.2)	9.5 (6.5-18.4)	0.7 (-7.2 to 4.9)	17.4 (9.9- 25.2)	14.8 (6.1-16.8)	-0.2 (-8.9 to 3.0)	0.64

Table 4.8: Pairwise analysis of daytime (07:00-22:00) glycaemic outcomes for baseline users of RT-CGM/ isCGM and SMBG in the **control arm**.

All values median (IQR).

Abbreviations: SMBG (self-monitoring blood glucose); RT-CGM (real-time continuous glucose monitoring); isCGM (intermittently-scanned continuous glucose monitoring)

	Baseline user SMBG (n = 18)			Baseline user RT-CGM or isCGM (n = 15)			P value (RT-CGM/isCGM vs SMBG)
	Pre-intervention	Last 2 weeks intervention	Change	Pre-intervention	Last 2 weeks intervention	Change	
% TIR 3.9-10 mmol/L (70-180 mg/dL)	52.0 (45.1-59.9)	49.6 (46.0-57.5)	-0.7(-8.0 to 3.3)	50.7 (40.3-62.4)	52.1 (47.2-59.9)	1.6 (-1.9 to 6.8)	0.22
% TIR 3.9-7.8 mmol/L (70-140 mg/dL)	30.3 (22.8-36.5)	29.1 (27.4-31.5)	0.7 (-8.7 to 4.6)	28.5 (17.9-35.4)	27.9 (22.1-37.9)	4.4 (-4.9 to 8.3)	0.25
% TBR < 3.9 mmol/L (<70 mg/dL)	2.1 (0.5-4.3)	1.9 (1.2-3.0)	-0.4 (-1.7 to 0.8)	0.7 (0.4-1.9)	1.3 (0.4-1.7)	0.2 (-0.3 to 0.6)	0.13
% TBR < 3.0 mmol/L (<54 mg/dL)	0.2 (0.0-0.8)	0.2 (0.1-0.7)	-0.1 (-0.3 to 0.1)	0.1 (0.0-0.3)	0.1 (0.0-0.3)	0.0 (-0.2 to 0.1)	0.43
% TBR < 2.8 mmol/L (<50 mg/dL)	0.2 (0.0-0.6)	0.1 (0.0-0.5)	-0.1 (-0.3 to + 0.1)	0.1 (0.0-0.2)	0.0 (0.0-0.1)	0.0 (-0.2 to 0.0)	0.73
% TAR >10 mmol/L (> 180 mg/dL)	42.9 (34.4-50.6)	47.5 (38.8 – 51.1)	0.2 (-3.1 to 7.9)	47.2 (36.0-58.3)	44.9 (37.8-50.6)	-1.7 (-6.8 to 1.2)	0.17
% TAR > 13.9 mmol/L (>250 mg/dL)	13.3 (6.9-17.7)	14.5 (9.4-20.3)	1.3 (-1.5 to 4.5)	13.5 (6.7-20.3)	15.1 (7.8-19.4)	0.5 (-2.8 to 2.8)	0.29

Table 4.9: Pairwise analysis of daytime (07:00-22:00) glycaemic outcomes for baseline users of RT-CGM/ isCGM and SMBG in the **intervention (ABC4D) arm**.

All values median (IQR).

Abbreviations: isCGM (intermittently-scanned continuous glucose monitoring); RT-CGM (real-time continuous glucose monitoring); SMBG (self monitoring blood glucose)

4.2.6 Hypoglycaemia events

The change in the number of hypoglycaemia events per day did not differ between ABC4D and control during the daytime (0 (0 to -1) versus 0 (0 to -1) respectively; p = 0.70) or night-time (0 (0 to 0) versus 0 (0 to 0); p = 0.40) (Table 4.10). A within group difference was demonstrated in the control arm during the daytime, with a reduction in the number of hypoglycaemia events from 1 (0 to 1) pre-control to 0 (0 to 1) during last 2 weeks of control; p = 0.02 (Table 4.10). A within group difference was not found with ABC4D either during the daytime or night-time.

	Pre-control	Last 2 weeks of control	Change control	P value last 2 weeks of control vs pre control	Pre-intervention	Last 2 weeks of intervention	Change intervention	P value last 2 weeks of intervention vs pre-intervention	P value change intervention vs change control
Daytime (07:00-22:00)	1 (0-1)	0 (0-1)	0 (-1 to 0)	**0.02**	1 (0-2)	0 (0-1)	0 (-1 to 0)	0.11	0.70
Night-time (22:00-07:00)	0 (0-1)	0 (0-1)	0 (0 to 0)	0.41	0 (0- 0)	0 (0-1)	0 (0 to 0)	0.44	0.40

Table 4.10: **Number of hypoglycaemia events per day for the control and intervention periods** (defined as consecutive glucose readings <3.0 mmol/L for at least 20 minutes separated by at least 30 minutes of consecutive glucose readings ≥ 3.0 mmol/L between events). Results presented as median (IQR) (n = 33).

4.2.7 HbA1c and Glucose Management Index

For participants recruited remotely with a complete set of HbA1c results (n=17), the HbA1c change was not different during ABC4D compared to control (2 (-2 to 6) mmol/L versus -2 (-5 to 2); p = 0.11) (Table 4.11). The change in glucose management indicator (GMI) (n=33) with ABC4D compared to control was not significantly different (+1.1 (-2.2 to 2.2) mmol/L ABC4D versus (-1.1 (-2.2 to 3.3) mmol/L control; p = 0.57) (Table 4.12). There were no within group differences in GMI for ABC4D or control (Table 4.12).

	Pre control	Post control	Change control	Pre intervention	Post intervention	Change intervention	P value change in HbA1c intervention vs control
HbA1c (mmol/mol)	60 (58-64)	60 (54-67)	-2 (-5 to 2)	59 (55-66)	62 (55-64)	2 (-2 to 6)	0.11
HbA1c (%)	7.6 (7.5-8.0)	7.6 (7.1-8.3)	-0.2 (-0.5 to 0.2)	7.5 (7.2-8.2)	7.8 (7.2-8.0)	0.2 (- 0.2 to 0.5)	

Table 4.11: **Change in HbA1c**

Results presented as median (IQR) (n =17).

	2 weeks pre-control	Last 2 weeks control	Change control	P value last 2 weeks of control vs pre control	2 weeks pre-intervention	Last 2 weeks intervention	Change intervention	P value last 2 weeks of intervention vs pre intervention	P value change intervention vs change control
GMI (%)	7.6 (7.1-8.0)	7.5 (7.2-8.0)	-0.1 (-0.2 to 0.3)	0.75	7.5 (7.3-8.0)	7.6 (7.3-8.0)	0.1 (-0.2 to 0.2)	0.62	0.57
GMI (mmol/mol)	59.6 (54.1-63.9)	58.5 (55.2-63.9)	-1.1 (-2.2 to 3.3)		58.5 (56.3-63.9)	59.6 (56.3-63.9)	1.1 (-2.2 to 2.2)		

Table 4.12: Change in Glucose Management Indicator (GMI)

Results presented as median (IQR) (n = 33)

4.3 Quality of Life and Hypoglycaemia Awareness Questionnaire Outcomes

There were complete questionnaire sets available for 32 participants (Table 4.13). The Diabetes treatment satisfaction questionnaire (DTSQ) demonstrated relatively high levels of diabetes treatment satisfaction at baseline (median (IQR) score 28 (22-31)). A smaller increase in DTSQ score was observed post ABC4D compared to post control from baseline (+2 (-3 to +9) versus +3.5 (0.5 to 9.5); p = 0.03) (Table 4.13). There was an increase in DTSQ score within the control group (baseline 28 (22-31) versus post control 31 (29-33.5); p = 0.0004). There was no within group difference in DTSQ score observed with ABC4D. There were no differences between ABC4D and control in terms of the change in perceived fear of hypoglycaemia or hyperglycaemia scores on the DTSQ questionnaire from baseline. There were no within group changes in perceived fear of hypoglycaemia or hyperglycaemia scores for ABC4D or control.

The Problem Areas in Diabetes (PAID) questionnaire showed relatively low levels of diabetes related emotional distress at baseline (median (IQR) score 18.8 (10-41.3)). No differences were observed in change in PAID score from baseline to post ABC4D compared to post control (1.3

(-2.5 to 9.4) versus -1.25 (-5 to +5); p = 0.62) (Table 4.13). There were no within group differences in PAID scores for ABC4D or control (Table 4.13).

The Diabetes Quality of Life Questionnaire (DQOL) demonstrated no difference between ABC4D and control in the change in scores from baseline for the satisfaction, impact, social/vocational worry or diabetes related worry sections or global scores (Table 4.13). There were no within group differences for ABC4D or control in any of the DQOL section scores or the global score (Table 4.13). Data from 17 participants were excluded from the DQOL social/vocational worry sub-section analysis, as they had marked more than 2 of the 7 items as not applicable in at least one of the DQOL questionnaires they completed during the study, as per the scoring system proposed by Jacobson et al (230).

The change in GOLD score post ABC4D compared to post control from baseline did not differ significantly (0 (0 to + 1) versus 0 (-0.8 to +1); p = 0.65) (Table 4.13). There were no within group differences in GOLD score for ABC4D or control (Table 4.13).

	Baseline	Post control	Change in score post control compared to baseline	P value post control versus baseline	Post intervention	Change in score post intervention compared to baseline	P value post intervention vs baseline	P value change intervention vs change control
DTSQ total score	28 (22-31)	31 (29-33.5)	3.5 (0.5 to 9.5)	**0.0004**	29 (25.5-34)	2 (-3 to 9)	0.12	**0.03**
Perceived fear of hyperglycaemia	3.5 (2-4)	4 (2-4)	0 (-1 to 1)	0.59	4 (3-4)	0 (0 to 1)	0.17	0.68
Perceived fear of hypoglycaemia	2 (1-3)	2 (1-3)	0 (-0.5 to 0.5)	0.94	2 (1-4)	0 (0 to 1)	0.18	0.31
PAID score	18.8 (10-41.3)	22.5 (11.3-33.8)	-1.25 (-5 to +5)	0.61	23.1 (11.3-29.4)	1.3 (-2.5 to 9.4)	0.21	0.62
DQOL satisfaction*	68.3 (57.5-80)	71.7 (61.7-78.3)	3.3 (-3.3 to 8.1)	0.15	71.7 (57.5-76.7)	1.7 (-5 to 7.5)	0.60	0.34
DQOL impact*	70.9 (64.4-78.2)	71.3 (66.3-78.8)	2.4 (-2.5 to 5)	0.07	72.5 (63.8 - 80)	0 (-2.5 to 3.8)	0.44	0.25
DQOL worry: social/vocational (n=15)**	75.0 (50-92.9)	67.9 (50-91.7)	-1.2 (-10.7 to 12.5)	0.91	67.9 (54.2-83.3)	0.0 (-9.5 to 7.1)	0.82	0.63
DQOL worry: diabetes related (n=32)**	75.0 (61.5-82.3)	71.9 (57.3-83.3)	-1.0 (-10.4 to 10.4)	0.60	71.9 (60.4-83.3)	0 (-8.3 to 7.3)	0.70	0.62
DQOL global score (n=15)***	69.6 (62.0-78.3)	69.6 (62.5-77.3)	-0.1 (-2.2 to 7.1)	0.48	70.4 (60.9-78.7)	0.5 (-1.1 to 6.3)	0.38	0.89
GOLD	2 (1.5-2.25)	2 (2-3)	0 (-0.8 to 1)	0.44	2 (2-3)	0 (0 to 1)	0.25	0.65

Table 4.13: Quality of life questionnaire and GOLD scores

Adapted with permission from Unsworth et al (219), with the additions of DQOL scores and within group differences for all questionnaires

All values median (IQR)

n=32 complete questionnaire sets unless otherwise stated.

*All participants with complete questionnaire sets (n=32) answered at least 12 of the 15 satisfaction items and at least 16 of the 20 impact items (criteria proposed by Jacobson et al (230).

**Participants responses included if they provided a 1-5 score for at least 5 out of the 7 social/vocational worry items or at least 2 of the 4 diabetes related worry items or (as proposed by Jacobson et al (230)) on all DQOL questionnaires completed at baseline, post 1st treatment phase and post 2nd treatment phase.

***Global scores included if at least 2 of the 4 diabetes related worry items and at least 5 out of the 7 social/vocational worry items scored 1-5 on all DQOL questionnaires completed at baseline, post 1st treatment phase and post 2nd treatment phase.

Abbreviations: Diabetes Quality of Life questionnaire (DQOL), Diabetes Treatment Satisfaction Questionnaire (DTSQ), Problem Areas in Diabetes questionnaire (PAID).

4.4 Multiple Linear Regression

Multiple linear regression analysis demonstrated that the following variables did not influence change in daytime percentage TIR (3.9-10.0 mmol/L) with ABC4D; gender, duration of diabetes, age, baseline two weeks percentage TIR, baseline use of RT-CGM/isCGM or

percentage of submissions accepted by the ABC4D algorithm for inclusion in the case base for revision (Table 4.14).

	Coefficient
Gender	-3.14 (-9.41, 3.13)$^{0.31}$
Duration of diabetes	0.05 (-0.18, 0.29)$^{0.66}$
Age at screening	0.04 (-0.20, 0.28)$^{0.75}$
Baseline 2 weeks percentage TIR (3.9-10.0 mmol/L; 70-180mg/dL)	-0.16 (-0.41, 0.09)$^{0.21}$
Baseline use of RT-CGM/isCGM	-0.61 (-5.19, 6.40)$^{0.83}$
Percentage of submissions accepted by the algorithm	15.73 (-1.86, 33.33)$^{0.08}$

Table 4.14: **Multiple linear regression analysis of predictors of change in daytime (07:00-22:00) percentage TIR 3.9-10.0mmol/L from pre-intervention to the last 2 weeks of intervention** (n= 33). Coefficients with 95% confidence intervals are shown and significances in superscript.

Abbreviations: time in range (TIR); RT-CGM (real-time continuous glucose monitoring); isCGM (intermittently scanned continuous glucose monitoring)

4.5 ABC4D Outcomes

Apps uses, dose acceptance and discrepancy in doses

ABC4D outcomes were explored in a post-hoc analysis. During the last 2 weeks, the average number of apps uses (meals, snacks and correction doses) was higher with ABC4D compared to control (29.5 (23-32) versus 27 (20.5-30) p = 0.037) (Table 4.15). This difference was not observed with the average number for app uses for meal doses alone.

Participants accepted fewer doses (meals, snacks and correction doses) exactly as recommended by the algorithm during the last 2 weeks of ABC4D use compared to control (73.9 (53.3-95.1)% versus 83.3 (66.1-100)%; p = 0.02) (Table 4.15). Similarly, participants accepted a lower percentage of all doses during the last 2 weeks of ABC4D compared to control within 0.5 units of the recommendation (82.6 (65.0-96.6)% versus 90.5 (82.0-100)%; p = 0.02)

or within 1 unit of the recommendation (89.1 (75.3-97.8)% versus 93.8 (90.0-100)%; p = 0.006) (Table 4.15).

Participants accepted a lower percentage of meal submissions during the last 2 weeks of ABC4D use compared to control exactly as recommended by the algorithm (78.7 (55.8-97.6)% versus 93.5 (73.8-100)%; p = 0.009), within 0.5 units of the recommendation (85.2 (70.8-97.8) versus 95.7 (87.0-100); p = 0.004) and within 1 unit of the recommendation (91.5 (80.4-100) versus 97.7 (91.5-100); p = 0.006) (Table 4.15). Both the average meal dose recommended and the average meal dose taken did not differ significantly during the last 2 weeks between ABC4D and control (Table 4.15). Participants took a greater reduction in meal insulin dose from the recommended dose during the last 2 weeks of ABC4D compared to control (insulin dose discrepancy between dose recommended and dose recorded as taken -0.1 (-0.4 to 0.0) units ABC4D versus 0.0 (-0.2 to 0.0) units control; p = 0.011). This difference was also observed specifically in meals without exercise (-0.1 (-0.4 to 0.0) ABC4D versus 0.0 (-0.2 to 0.0) control; p = 0.017) but not observed in meals with exercise (Table 4.15).

	Control last 2 weeks	Intervention last 2 weeks	P value last 2 weeks intervention vs last 2 weeks control
All participants (n =33)			
Average number of all app uses[a] per week	27 (20.5-30)	29.5 (23-32)	**0.037**
Average number of app meal uses per week (>10g)	22 (17-24.5)	21.5 (19.5-26.5)	0.07
Participants with ≥ 1 meal submission (>10g) in both the last 2 weeks of the control and last 2 weeks of the intervention periods (n = 31)			
% All doses[a] accepted as recommended by participant	83.3 (66.1-100)	73.9 (53.3-95.1)	**0.02**
% All doses[a] accepted within 0.5 unit by participant	90.5 (82.0-100)	82.6 (65.0-96.6)	**0.02**
% All doses[a] accepted within 1 unit by participant	93.8 (90.0-100)	89.1 (75.3-97.8)	**0.006**
% Meal doses accepted as recommended by participant	93.5 (73.8-100)	78.7 (55.8-97.6)	**0.009**
% Meal doses accepted within 0.5 units by participant	95.7 (87.0-100)	85.2 (70.8-97.8)	**0.004**
% Meal doses accepted within 1.0 units by participant	97.7 (91.5-100)	91.5 (80.4-100)	**0.006**
Meal submission average dose recommended	6.1 (4.8-8.6)	6.2 (4.6-9.8)	0.34
Meal submission average dose taken	6.1 (4.5-8.6)	5.8 (4.5-9.7)	0.68
Insulin dose discrepancy for all meal submissions	0.0 (-0.2 to 0.0)	-0.1 (-0.4 to 0.0)	**0.011**
Insulin dose discrepancy for meal submissions without exercise	0.0 (-0.2 to 0.0)	-0.1 (-0.4 to 0.0)	**0.017**
Insulin dose discrepancy for meal submissions with exercise[b] (n =15)	0.0 (-0.5 to 0.0)	-0.2 (-0.5 to 0.0)	0.23

Table 4.15: App usage, insulin dose acceptance rate and magnitude of discrepancy between doses recommended and doses participants recorded as taken. Reproduced with permission from Unsworth et al (219)

All values median (IQR).

[a]All doses includes insulin doses for meals (>10g), snacks (≤10g) and correction doses

[b]Data for participants with ≥ 1 meal submission (>10g) **with exercise** in both the last 2 weeks of the control and last 2 weeks of the intervention periods (n = 15)

Correlation between average number of meal uses per week for the last 2 weeks or entire duration of ABC4D/control and change in daytime glycaemic variables

I created scatter graphs to examine the correlation between the average number of app meal uses (>10g) over the last 2 weeks or entire duration of intervention/control phases and change in daytime percentage TIR (3.9-10mmol/L, 70-180mg/dL), percentage time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL), percentage TBR (< 3.0mmol/L; < 54mg/dL) or percentage TAR (>10mmol/L; 180mg/dL) (Figures 4.2, 4.3, 4.4 and 4.5). Visual inspection suggested a possible correlation between the average number of meal app uses per week during the last 2 weeks of the intervention period (Figure 4.3c) or whole intervention period (Figure 4.5c) and change in daytime percentage TBR <3.0 mmol/L. However linear regression analysis demonstrated that the average number of meal app uses per week during the last 2 weeks of the intervention period did not influence the change in daytime percentage TBR <3.0 mmol/L (co-efficient -0.011, 95% CI -0.044 to 0.020, p =0.46). Similarly linear regression analysis showed that the average number of meal app uses per week during the whole intervention period did not influence the change in daytime percentage TBR <3.0 mmol/L (co-efficient -0.011, 95% CI -0.048 to 0.025, p =0.53).

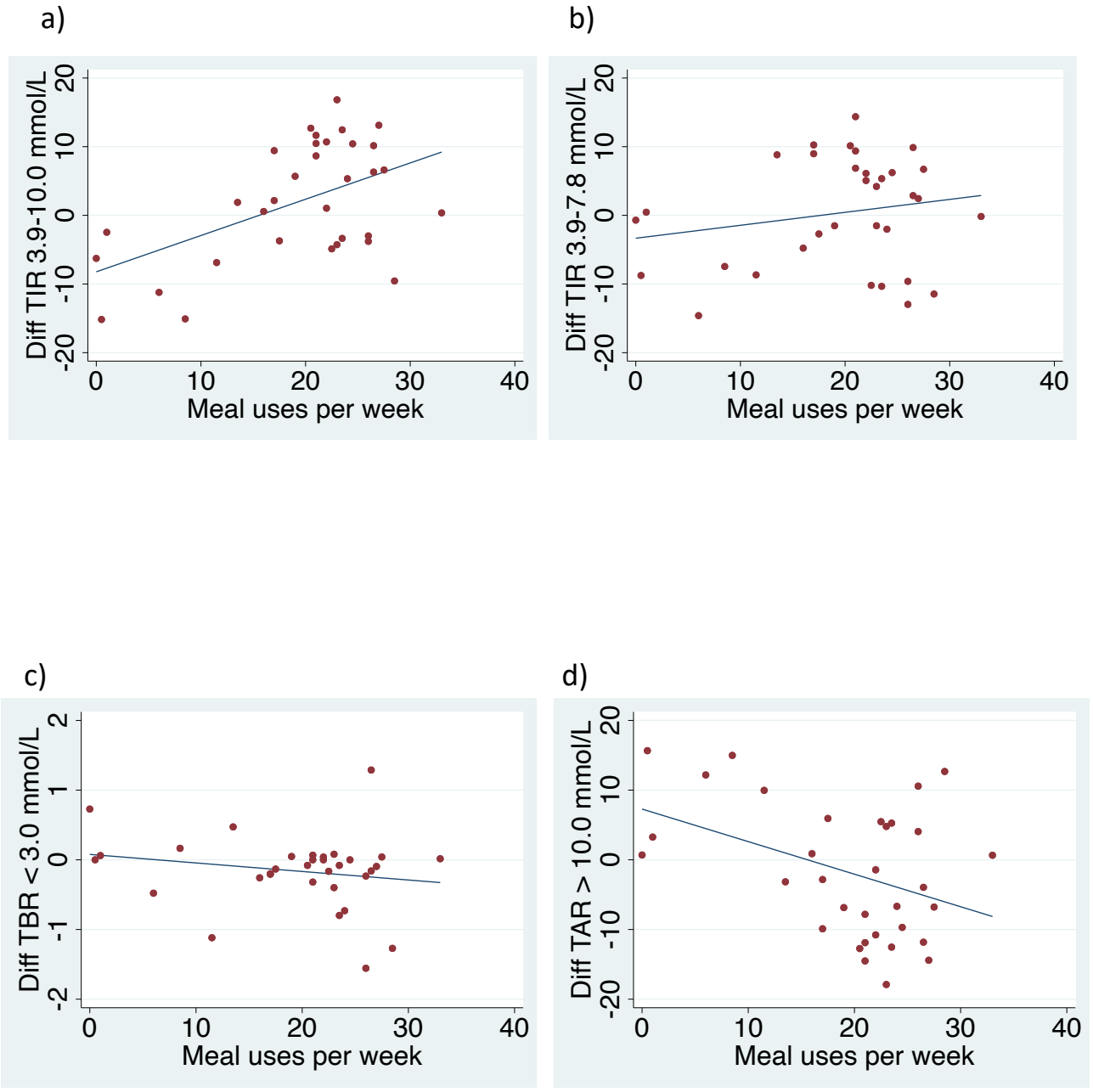


Figure 4.2: Scatter graphs to investigate the correlation between average number of app meal (>10g) uses per week during the **last 2 weeks of the control period** and daytime glycaemic outcomes:

a) change in percentage time in range (TIR) (3.9-10mmol/L, 70-180mg/dL)

b) change in percentage time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL)

c) change in percentage time below range (TBR) (< 3.0mmol/L; < 54mg/dL)

d) change in percentage time above range (TAR) (>10mmol/L; 180mg/dL)

Lines of best fit have been added. Abbreviation: Difference (Diff)

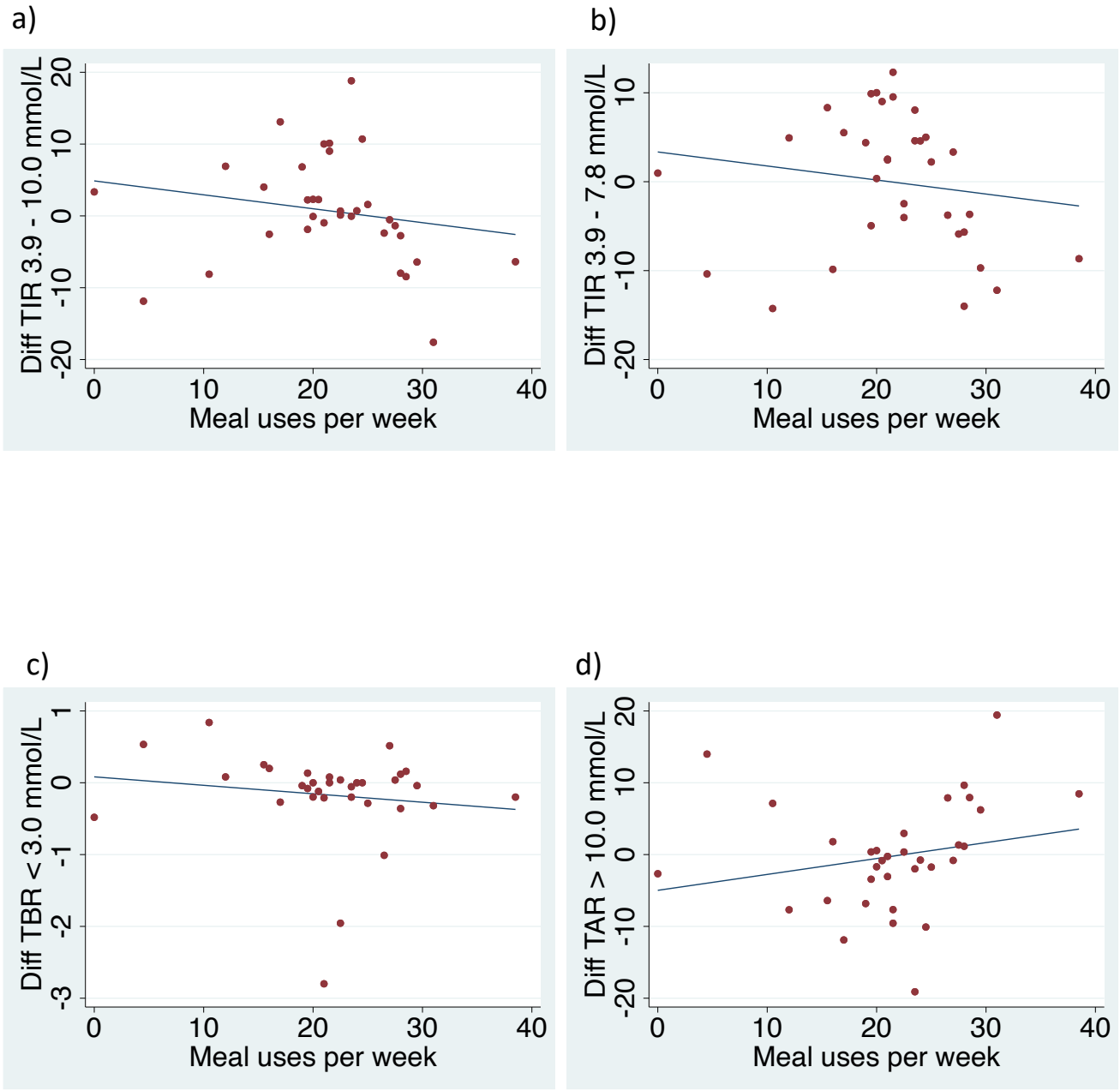


Figure 4.3: Scatter graphs to investigate the correlation between average number of app meal (>10g) uses per week during the **last 2 weeks of the intervention period** and daytime glycaemic outcomes:

a) change in percentage time in range (TIR) (3.9-10mmol/L, 70-180mg/dL)

b) change in percentage time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL)

c) change in percentage time below range (TBR) (< 3.0mmol/L; < 54mg/dL)

d) change in percentage time above range (TAR) (>10mmol/L; 180mg/dL)

Lines of best fit have been added. Abbreviation: Difference (Diff)

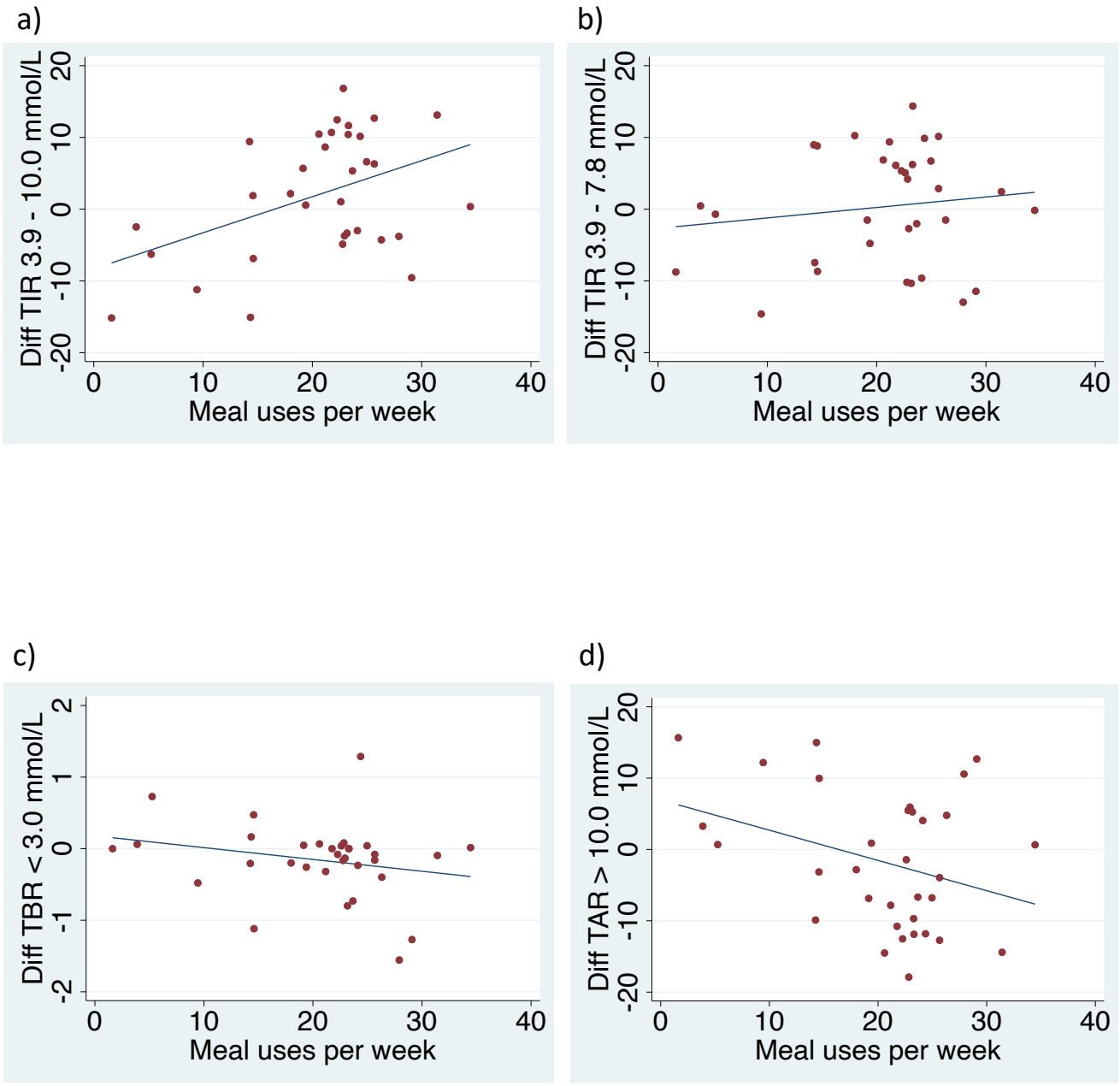


Figure 4.4: Scatter graphs to investigate the correlation between average number of app meal (>10g) uses per week during the **whole control period** and daytime glycaemic outcomes:

a) change in percentage time in range (TIR) (3.9-10mmol/L, 70-180mg/dL)

b) change in percentage time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL)

c) change in percentage time below range (TBR) (< 3.0mmol/L; < 54mg/dL)

d) change in percentage time above range (TAR) (>10mmol/L; 180mg/dL)

Lines of best fit have been added. Abbreviation: Difference (Diff)

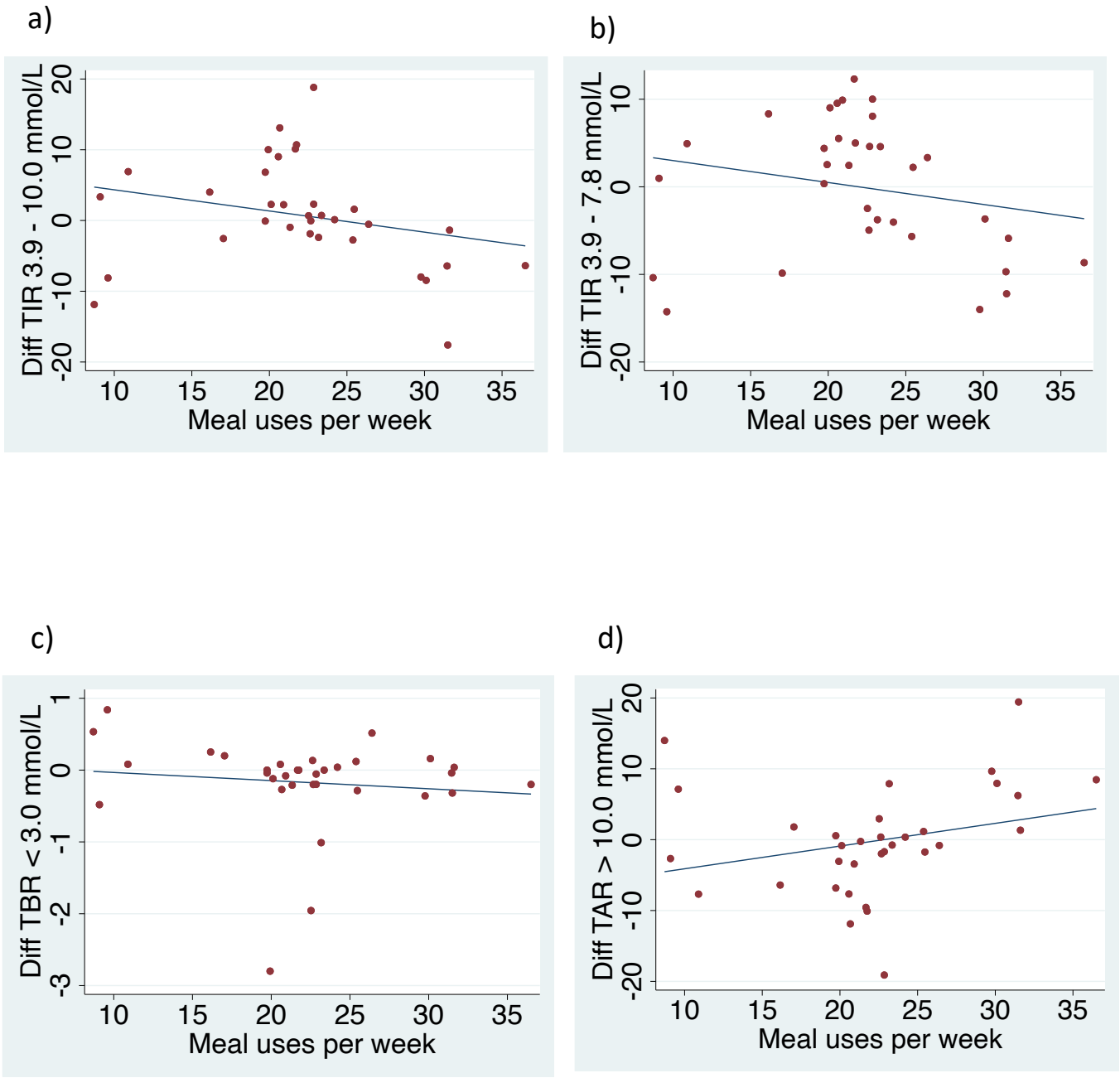


Figure 4.5: Scatter graphs to investigate the correlation between average number of app meal (>10g) uses per week during the **whole intervention period** and daytime glycaemic outcomes:

a) change in percentage time in range (TIR) (3.9-10mmol/L, 70-180mg/dL)

b) change in percentage time in euglycaemia (3.9-7.8mmol/L; 70-140mg/dL)

c) change in percentage time below range (TBR) (< 3.0mmol/L; < 54mg/dL)

d) change in percentage time above range (TAR) (>10mmol/L; 180mg/dL)

Lines of best fit have been added. Abbreviation: Difference (Diff)

Insulin to carbohydrate ratios at the start and end of the intervention phase

Table 4.16 and Figure 4.6 show the final and initial insulin to carbohydrate ratios (ICRs) in the intervention phase for breakfast, lunch and dinner with and without exercise. The final ICR for lunch with exercise was significantly lower than the initial ICR (12.5 (9.5-14.3) versus 14.3 (10.0-14.3); p = 0.03), therefore recommending a larger insulin dose. Similarly, the final ICR for dinner with exercise was lower than the initial ICR (12.0 (8.7 to 14.1) versus 14.3 (9.6 to 14.3); p = 0.001). Figure 4.7 shows the individual pairwise initial and final breakfast, lunch and dinner ICRs without exercise (a) and with exercise (b) in the adaptive arm.

	Breakfast (without exercise)	Lunch (without exercise)	Dinner (without exercise)	Breakfast with exercise	Lunch with exercise	Dinner with exercise
Initial ICR	10.0 (6.0-10.0)	10.0 (7.0-10.0)	10.0 (6.7 – 10.0)	14.3 (8.6-14.3)	14.3 (10.0-14.3)	14.3 (9.6 to 14.3)
Final ICR	8.5 (5.4-11.5)	8.9 (7.6-10.6)	8.4 (5.5-10.0)	12.9 (8.6-14.3)	12.5 (9.5-14.3)	12.0 (8.7 to 14.1)
Absolute change in ICR	0.3 (-0.5 to 1.5)	-0.3 (-1.5 to 1.7)	-0.5 (-1.7 to 0.4)	0.0 (-0.4 to 0.0)	-0.1 (-1.4 to 0.0)	-0.5 (-1.3 to 0.0)
P value final ICR vs initial ICR	0.32	0.80	0.09	0.34	0.03	0.001

Table 4.16: ICR changes in the adaptive arm

All values median (IQR).

*Wilcoxon signed rank test used to evaluate differences in final and initial ICRs.

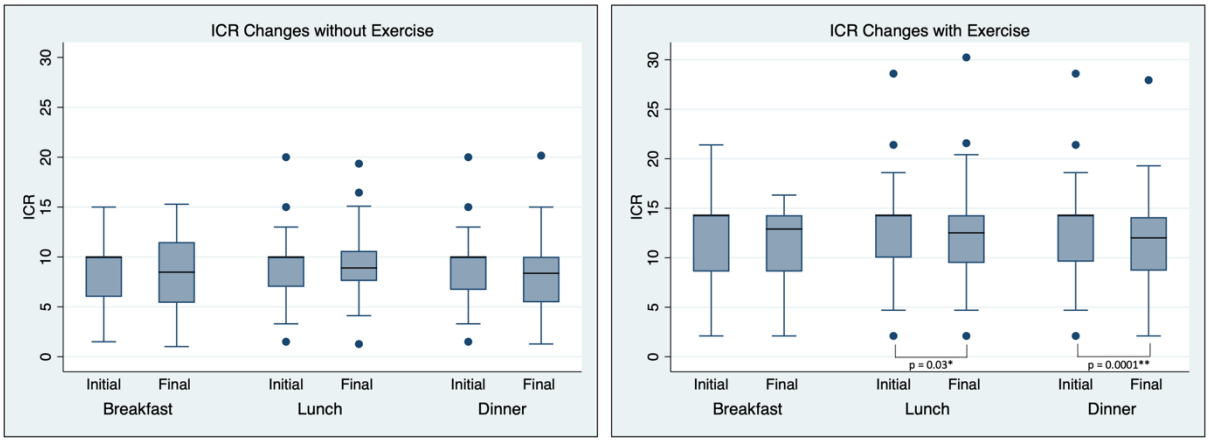


Figure 4.6: Initial and Final ICRs in the intervention phase for Breakfast, Lunch and Dinner a) without exercise (n = 33) b) with Exercise (n = 33)

Reproduced with permission from Unsworth et al (219)

The dots represent ICRs which were outliers.

The median is represented by a horizontal black line. It is the same value as the 75th percentile for the initial breakfast ICR, initial lunch ICR and initial dinner ICR both without and with exercise (all 1 unit:10g without exercise and 1unit:14.3g with exercise).

*The difference between final and initial lunch with exercise ICR was statistically significant (12.5 (9.5-14.3) vs 14.3 (10-14.3); p = 0.03)

** The difference between final and initial dinner with exercise ICR was statistically significant (12.0 (8.7-14.1) vs 14.3 (9.6-14.3); p = 0.001)

Abbreviations: ICR (insulin to carbohydrate ratio)

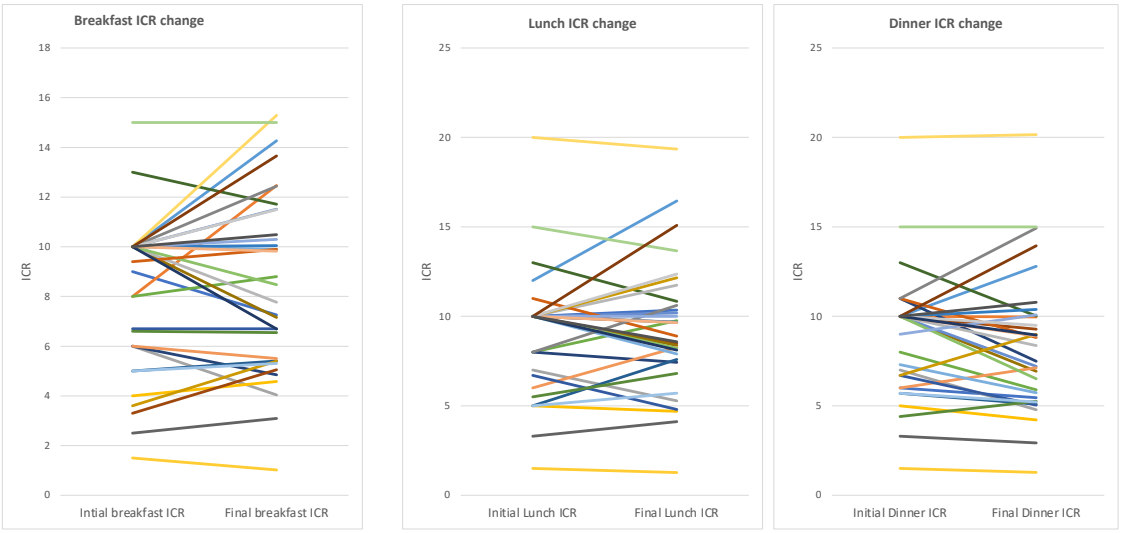


Figure 4.7 a) Individual pairwise initial and final breakfast, lunch and dinner ICRs **without exercise** selected in the adaptive arm (n=33)

Abbreviations: insulin to carbohydrate ratio (ICR)

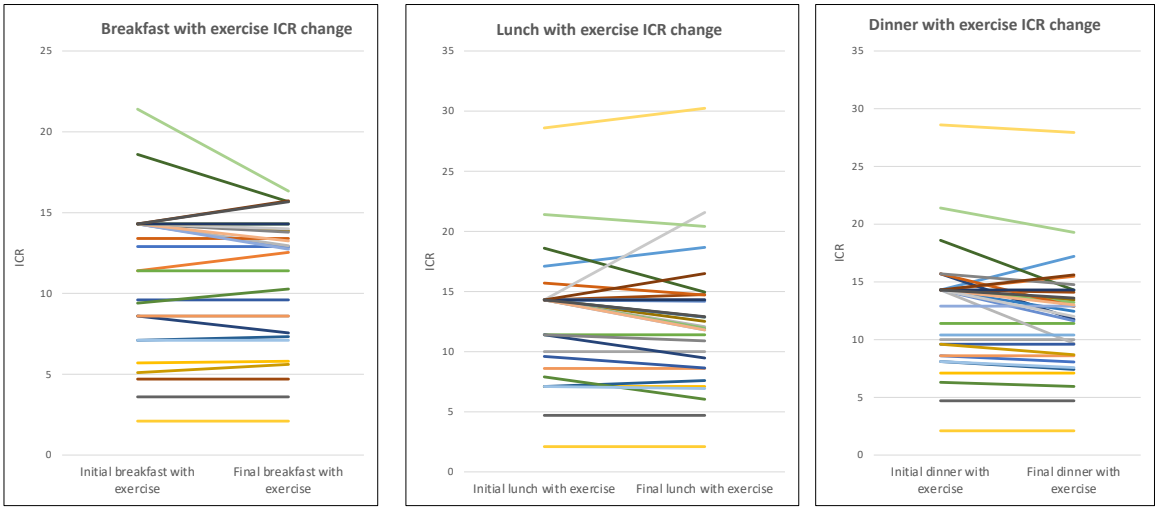


Figure 4.7 b) Individual pairwise initial and final breakfast, lunch and dinner ICRs **with exercise selected** in the adaptive arm (n=33)

Abbreviations: insulin to carbohdyrate ratio (ICR)

Case parameter selection

Participants selected the case parameter of exercise most frequently (pre and or post meal) (median (IQR) 18.6% (10.5-38.5)% of submissions) (Table 4.17). Delayed bolus was selected in 4.1% (1.8-8.3)% of submissions. The pre-menstrual cycle function was used by 4 out of 10 female participants of child-bearing age. These participants used the pre-cycle adjustment in 14.9% (3.3-26.5)% of submissions (Table 4.17).

	Submissions per participant in which case parameter selected (%)
Case parameters adjusting the insulin dose recommended (n =33)	
Exercise (pre and or post meal selected)	18.6 (10.5-38.5)
Delayed bolus[ab]	4.1 (1.9-8.3)
Pre- (menstrual) cycle (n = 4)[bc]	14.9 (3.3-26.5)
Case parameters not adjusting the insulin dose recommended (n =33)	
Dual bolus[bd]	0.0 (0.0- 0.2)
Alcohol	1.7 (0.2-9.2)
Stress	0.2 (0.0-0.7)
Slow meal	0.6 (0.2-2.5)

Table 4.17: Summary of percentage of submissions with case parameters selected

Data reported as median (IQR)

[a] Meal insulin only recommended without a correction dose or additional insulin if positive rate of change of glucose levels

[b] Submissions not included for adaptation

[c] Pre-(menstrual) cycle used by 4/10 (40%) of female participants of child-bearing age. One of these participants requested for it to be switched on at the 1 month review into the control phase and to manually activate, it was set to automatically be activated for the duration of the intervention period.

[d] Participants could write a note to explain they were going to split the dose (e.g. 50% now, 50% in 2 hours) but total dose recommended was not adjusted

Use of the note function

Table 4.18 summarises use of the note function within the app by participants. Fourteen participants submitted a note to inform of change in basal insulin, with median (IQR) 2 (1.25-3) days of use during the study. Eleven participants selected illness at least once during the study and five participants selected jetlag/sleeplessness at least once during the study (Table 4.18).

	Days of use (median (IQR)) (n = 33)	Days of use by participant if used ≥1 during the study (median (IQR))(number of participants using function)
Illness	0 (0-1)	2 (1-3) (n = 11)
Jetlag/sleeplessness	0 (0-0)	1 (1-3) (n = 5)
Change in basal insulin	0 (0-2)	2 (1.25-3) (n = 14)

Table 4.18: Summary of use of the note function

4.6 ABC4D Acceptability Questionnaire Outcomes

Data were analysed from 33 participants completing the ABC4D acceptability questionnaire at the end of the study. The questionnaire was divided into two sections: the first regarding the ABC4D application on a smartphone and the second regarding the ABC4D system as a whole (ABC4D application on a smartphone and CGM on a regular basis).

4.6.1 ABC4D application

All participants found the ABC4D main screen clear and easy to read and insulin on board (IOB) useful to view (Figure 4.8). The majority of participants found the colour scheme, button

size and symbols for glucose, meals and IOB acceptable (Figure 4.8). 84.8% of participants agreed or strongly agreed that entering data on the app screen, such as amount of carbohydrate and exercise, was straightforward. 15.2% of participants disagreed or strongly disagreed and 27.3% neither agreed or disagreed that there were enough options to describe the type, intensity and duration of exercise which they were about to undertake. Seven participants (21.2%) stated that they did not use the alcohol parameter. There were mixed opinions regarding whether entering alcohol intake was inconvenient; 33.3% disagreed or strongly disagreed, 21.2% neither agreed nor disagreed and 24.2% agreed with this statement (Figure 4.8). Selecting alcohol did not change the insulin bolus dose recommendation. 66.6% of participants agreed or strongly agreed with the statement that "it would be useful to enter additional information, such as type of alcohol (beer, wine, spirit), exercise description (e.g. running) or more speeds of meal absorption (e.g. fast/slow)." Free text box responses included suggestions to add type and quantity of alcohol, a description of the exercise type for both and planned exercise, such as walking or running, rather than aerobic or anaerobic, to add the time of exercise start after the meal and integrate data with the exercise tracker. Other suggestions included incorporating nutritional information into the app, adding the speed of meal absorption and improving the definition of "slow meal". However other participants felt that the information was sufficient and additional information would add complexity and increase the time burden, even if it may improve app accuracy. A point was raised that there are likely too many variables affecting glucose levels to account for anyway.

A later question focused more specifically on including additional parameters to actually adjust the insulin dose, compared to additional information to be provided as detailed above. In reference to the statement that it would be useful to include additional parameters for the ABC4D system to take into account when calculating an insulin dose recommendation, 51.7%

neither disagreed or agreed and 27.5% agreed or strongly agreed. Free text responses of suggestions for these parameters included a flag for hypo treatment and amount of carbohydrates consumed to treat the hypo, a conservative bedtime dose adjustment to reduce the risk of hypoglycaemia, adjusting for weather conditions and speed of carbohydrate absorption or glycaemic index of food. Ideas included incorporating a carbohydrate calculator using a specific food database and ability to input the weight of food or use a barcode scanner. Other suggestions included accounting for hormone fluctuations such as the dawn phenomenon, being able to input more information about recent exercise such as intensity and duration and the type and quantity of alcohol, being able to enter more detail for existing parameters or using parameters which were already included in the app such as alcohol and stress to actually adjust the insulin dose.

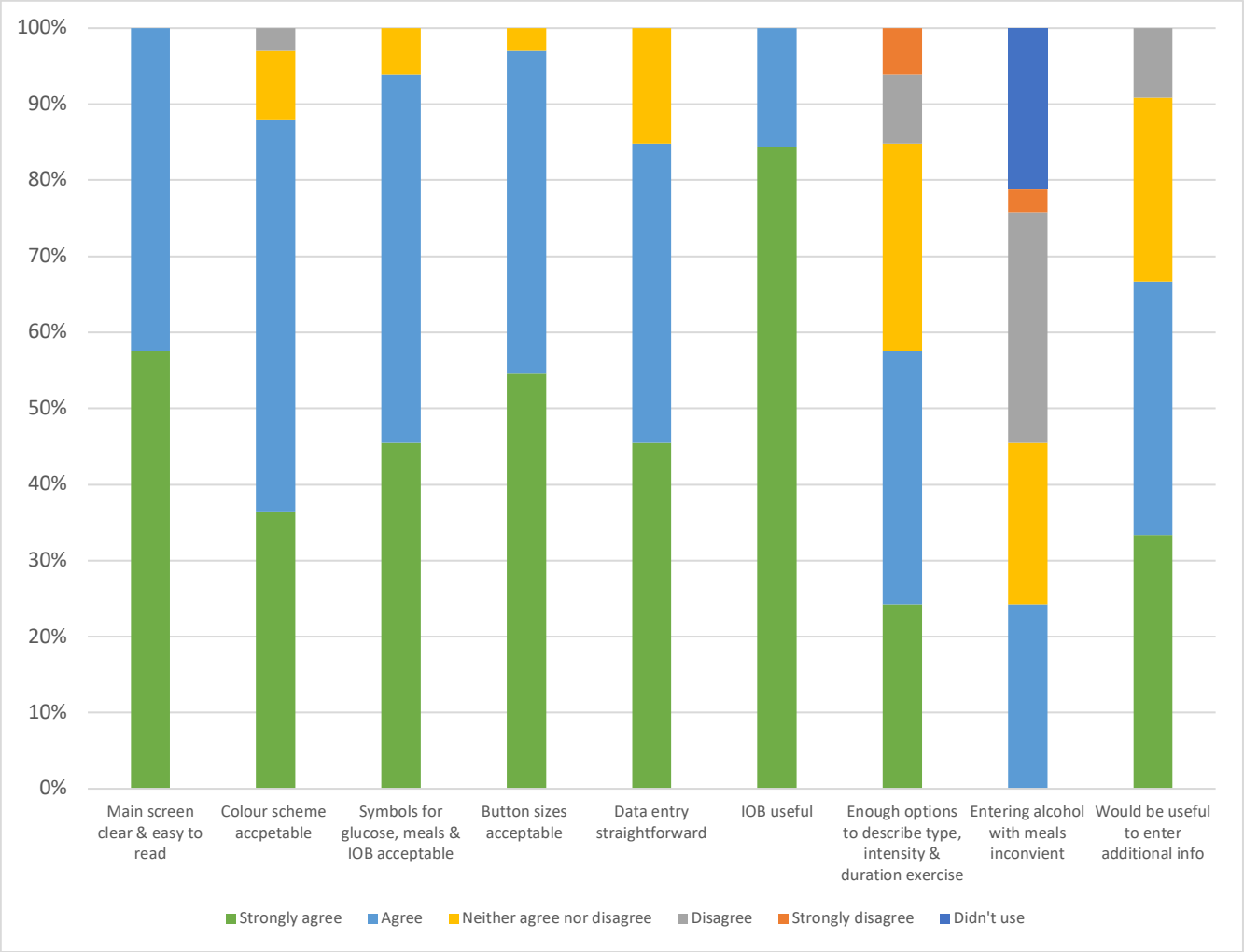


Figure 4.8: **Participants' responses to the questions regarding the ABC4D application taken from the ABC4D acceptability questionnaire completed at the end of the study**

n=33 except IOB question (n=32)

Recent and planned exercise were deemed to be the most useful features in the app, with 72.7% and 75.8% or participants respectively reporting that they found these parameters extremely or very useful. Alcohol, stress, slow meal and dual bolus were deemed less useful (Figure 4.9). In the notes tab, the comments tab was found to be most useful (51.5% rated as very or extremely useful), with a high proportion of participants reporting that they did not use the illness (60.6%), jetlag/sleeplessness (78.8%) or basal insulin dose change (66.7%) functions (Figure 4.9).

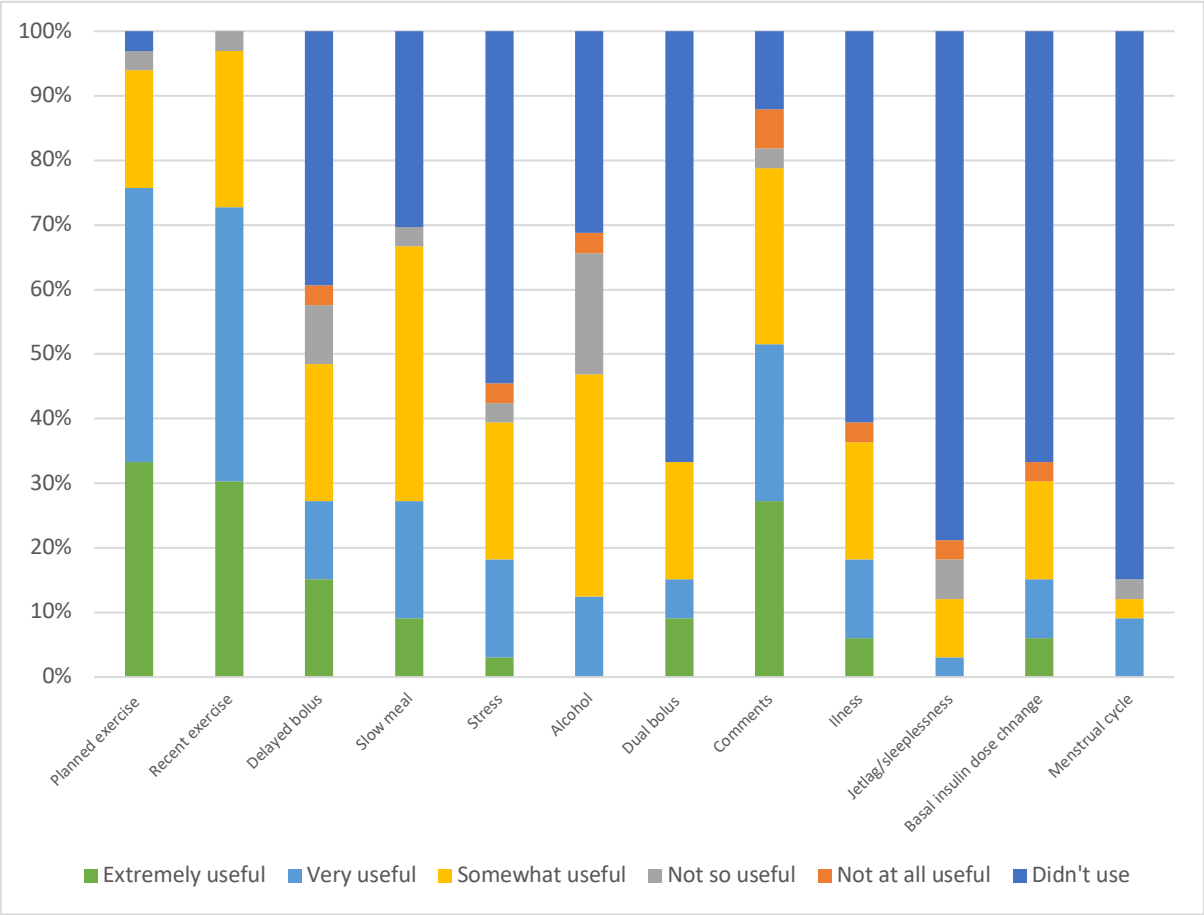


Figure 4.9: Participants' responses to the question "how useful did you find the following features" on the app, taken from the ABC4D acceptability questionnaire completed at study end

n=33 except alcohol (n= 32)

Figure 4.10 represents participants' level of agreement with statements regarding the continuous glucose monitoring trend arrow, logbook, graph and overall usability. The majority of participants (93.9%) found the CGM glucose arrow trend in the ABC4D app homepage useful. 81.8% of participants found it useful to be able to view previous doses and carbohydrate amounts in the logbook and 81.8% agreed or strongly agreed that the CGM meal and glucose information was saved and displayed in an easy to understand format in the logbook. Participants found the ABC4D app graph less useful; 39.4% neither disagreed or agreed and 57.6% strongly agreed or agreed with the statement that it was useful to be able to view a graph

of their sensor glucose levels with insulin doses and glucose setpoints. 93.9% overall considered the ABC4D application user-friendly/easy to use.

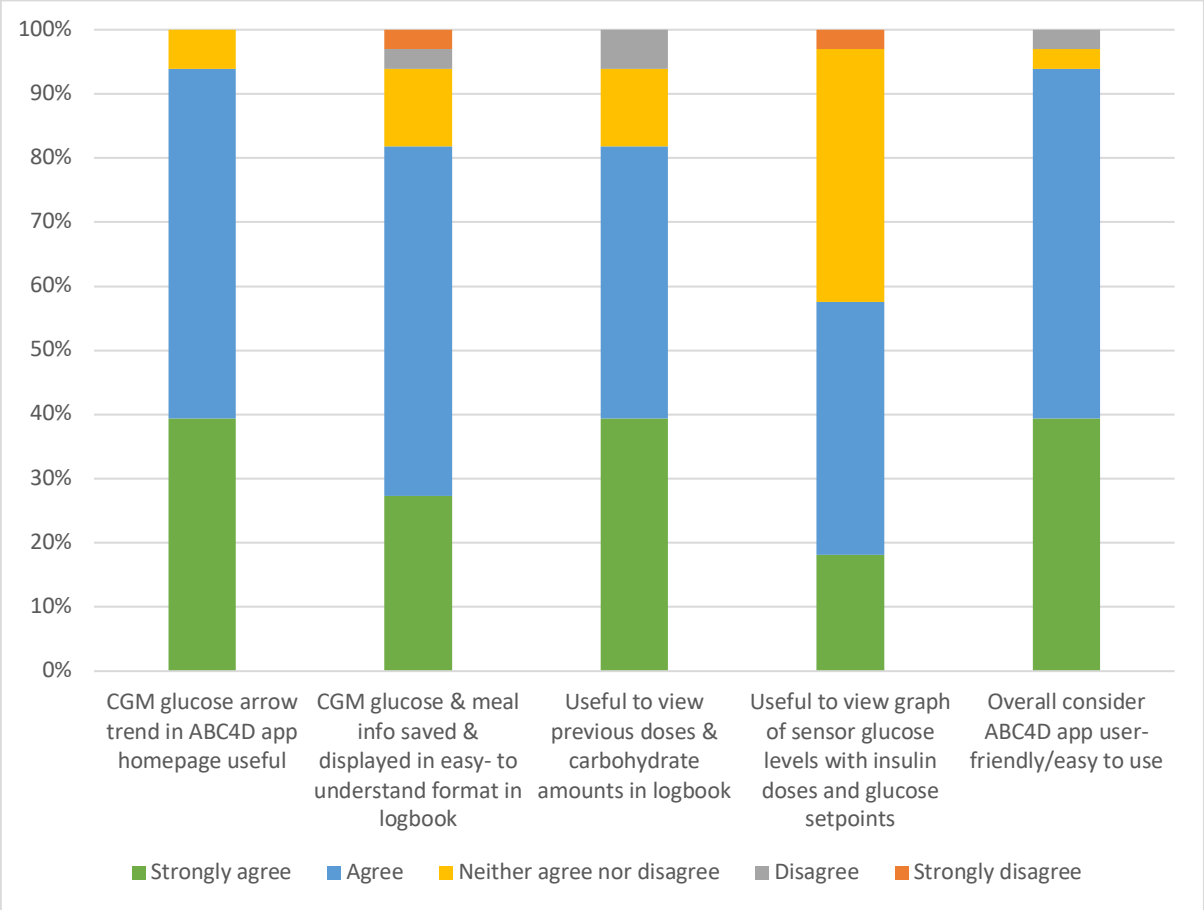


Figure 4.10: **Participants' level of agreement with statements regarding the continuous glucose monitoring trend arrow, logbook, graph and overall usability** (n=33)

Abbreviations: Continuous glucose monitoring (CGM)

4.6.2 The ABC4D System (ABC4D application on smartphone and Continuous Glucose Monitoring)

The majority of participants were not reluctant to use ABC4D whilst at work or travelling abroad (90.6% (n=32) and 90.9% (n=33) respectively) (Figure 4.11). 84.8% disagreed or strongly disagreed that they would be reluctant to use ABC4D before or after exercise. 87.9% were not reluctant to use ABC4D when eating out. There were mixed views on using the app

when unwell (Figure 4.11). Participants were least confident to use ABC4D when consuming alcohol, with 9.1% agreeing or strongly agreeing that they would be reluctant to use it and 15.2% neither agreeing or disagreeing.

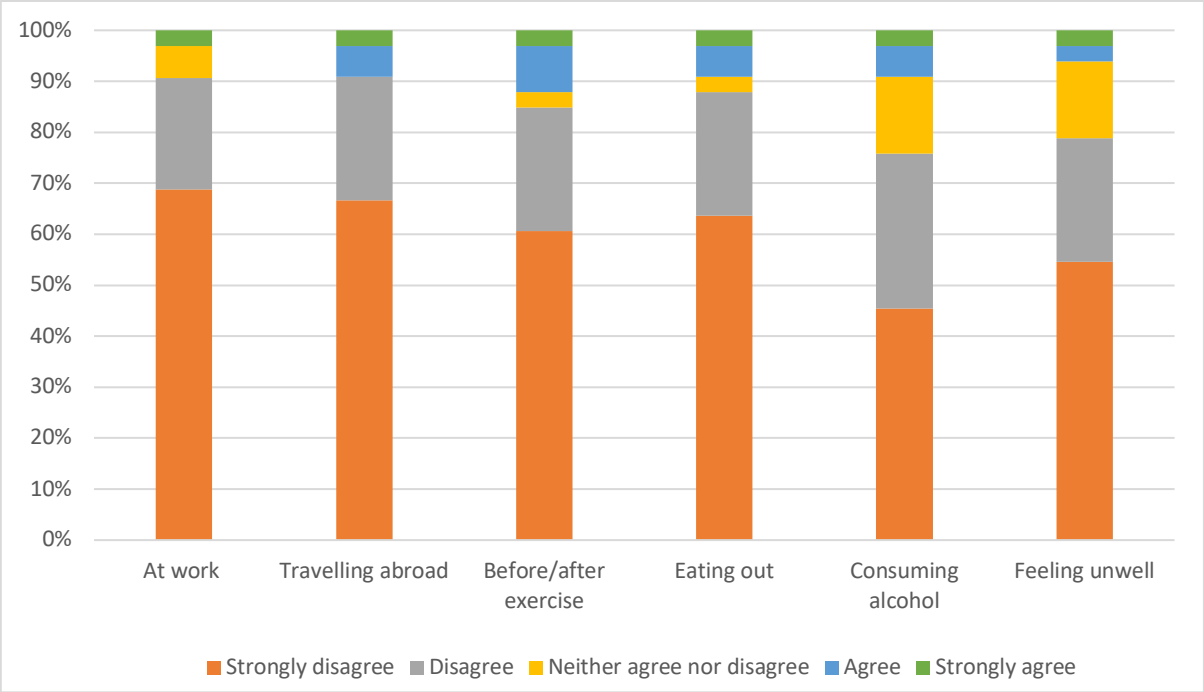


Figure 4.11: Participants' responses to the statement "I would be reluctant to use ABC4D in the following situations…" as part of the ABC4D acceptability questionnaire.

n=33 except for the statement at work (n=32)

Participants' level of agreement with statements regarding the ABC4D system as a whole are representing in Figure 4.12. All participants found it acceptable to wear CGM all the time. Most participants disagreed or strongly disagreed that using ABC4D for insulin calculation was more time consuming or caused more anxiety than their standard methd of bolus calculation (72.7% and 78.8% respectively). The responses of the participants to that statement that they checked the dose breakdown prior to accepting the dose recommendation varied;

48.5% agreed or strongly agreed, 48.5% disagreed or strongly disagreed and 3% (n=1) neither agreed nor disagreed. However 89.7% found being able to view the dose breakdown of an insulin dose recommendation useful. 81.8% trusted the insulin dose generated by ABC4D and 87.9% were overall happy to use the ABC4D system for bolus calcuation.

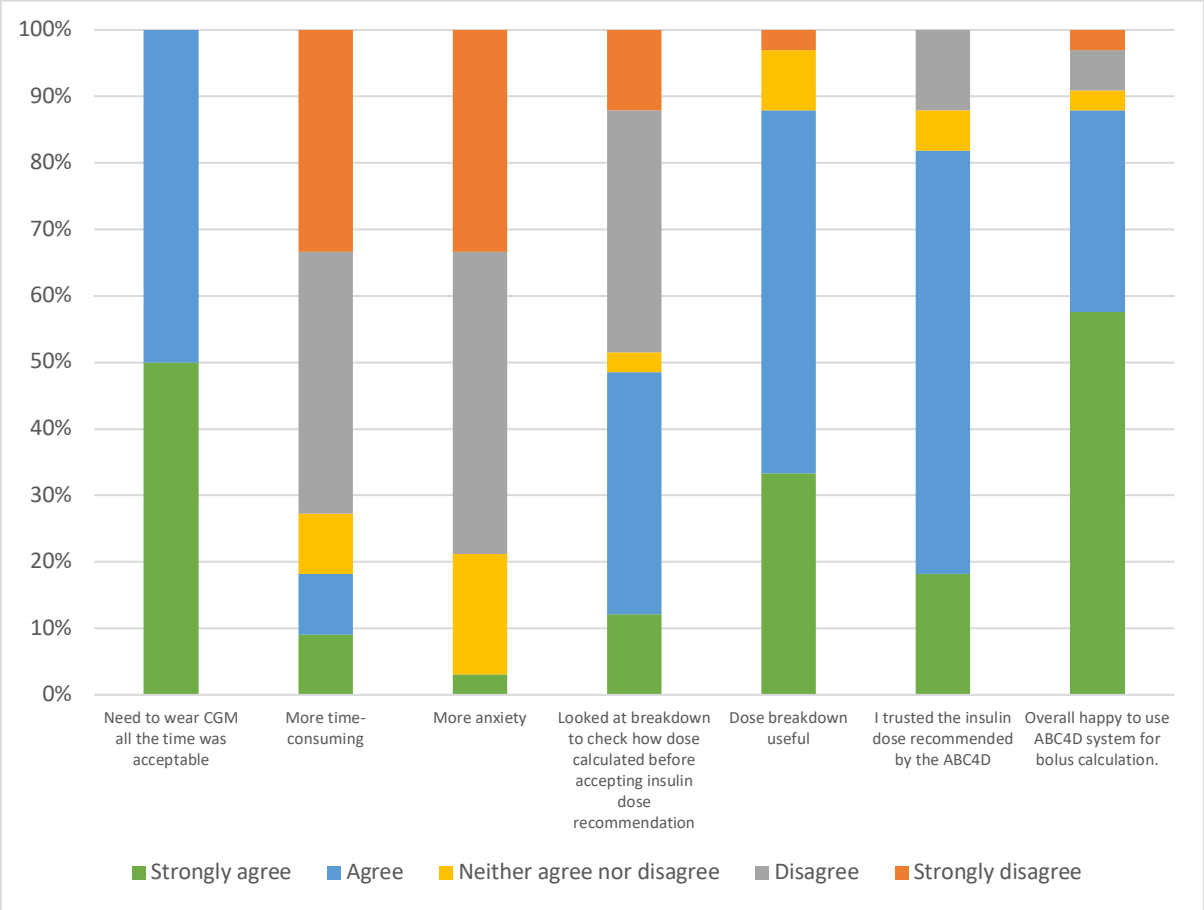


Figure 4.12: Participants' level of agreement with statements regarding the ABC4D system as part of the ABC4D acceptability questionnaire

n= 33 except for the statement regarding the need to wear CGM all the time n =32

There were no differences between ABC4D (adaptive bolus calculator) and control (non-adaptive bolus calculator) in participants' scores regarding whether they found the app more time consuming or anxiety provoking than their standard method of bolus calculation, whether they found viewing the dose breakdown useful and whether they were overall happy to use the system for bolus calculation (Table 4.19). There were no differences between adaptive and non-adaptive bolus calculator in terms of frequency of trusting the insulin dose recommendation and frequency of checking the dose breakdown prior to accepting the recommendation (Table 4.19).

	Control	Intervention	P value
Level of agreement statements*			
Using ABC4D for insulin calculation was more time consuming than using my standard method of bolus calculation (n=32)	2 (1.5-2.5)	2 (1-2.5)	0.74
Using ABC4D for insulin calculation caused more anxiety than using my standard method of bolus calculation (n=32)	2 (1-2)	2 (1-2)	0.35
It was useful to view the dose breakdown for an insulin dose recommendation	4 (4-5)	4 (4-5)	0.93
Overall, I would be happy to use the ABC4D system for bolus calculation	5 (4-5)	4.5 (4-5)	0.14
Frequency statements**			
I trusted the insulin dose recommendation generated by the ABC4D	4 (4-4)	4 (3.5-4)	0.15
Prior to accepting the insulin dose recommendation by ABC4D, I looked at the breakdown of how the dose was calculated to check this	4 (2-4)	4 (2-4)	0.62

Table 4.19: Participant scores (converted) for trust and usability statements comparing ABC4D to control. All values presented as median (IQR). N=31 unless otherwise stated (ABC4D questionnaire not completed (n=1), missing page (n=1)).

*Ordinal outcomes for level of agreement were converted to a score: strongly disagree = 1, disagree =2, neither agree nor disagree =3, agree =4, strongly agree =5.

**Ordinal outcomes for frequency were converted to a score: none of the time =1, some of the time =2, not sure =3, most of the time =4, each time =5.

4.6.4 Information provided regarding how to use the ABC4D system

All participants reported at the end of the first treatment phase that they had found the verbal instructions given on how to use the ABC4D system at the first consultation sufficient (n=32 completed questionnaires). In terms of agreement with the statement that the written user guide on how to use ABC4D was sufficient, 87.5% agreed or strongly agreed, 9.4% neither agreed or disagreed and 3.1% disagreed.

4.7 Adverse Events

Four adverse events occurred during the study, none of which were thought to be related to the intervention. One participant was withdrawn from the study during the control arm due to ongoing sensor site skin reactions which had not required medical intervention. Another participant experienced a likely sensor site infection which resolved without seeking medical attention during the intervention arm. One participant attended the emergency department after giving their basal insulin dose as bolus insulin by mistake during the intervention arm; this was managed by the participant with oral carbohydrate only and did not cause hypoglycaemia. One participant had two self-resolving nocturnal seizures, one seizure during the control arm and one seizure during the intervention arm. The participant was not hypoglycaemic at the time and had a background of epilepsy. There were no severe hypoglycaemia episodes and no serious adverse events reported.

4.8 ABC4D Software Updates Log

There were a number of updates made to the ABC4D software during the clinical trial in response to issues that I had observed on the ABC4D platform during routine checks or had been reported to me by participants (Table 4.20).

Version	Changes
R1.0	• *First release version*
R1.1	• *Fixed breakdown IOB*
R1.2	• *Fixed bug rounding control ISF* • *Rejection condition for previous meal changed to 1 hour*
R1.3	• *Fixed issue selecting control exercise ICRs*
R1.4	• *Fixed rare issue causing display of an old glucose value*
R1.5	• *Added rejection case for when user insulin differs from recommend*
R1.6	• *Fixed issue refreshing Recent exercise view* • *Added uploading version number and release ID with submissions*
R1.7	• *Added revising when user insulin higher than recommended and goes above target* • *increased insulin maximum to vary with carbohydrates consumed* • *Added ability for Clinicians to disable/enable app from settings* • *Fixed bug in insulin recommendation breakdown where negative ROC shows correction dose* • *Added emailing logs for remote debugging during setup*
R1.8	• *Added popup to check for late advice when significant ROC detected* • *Fixed time zone issue in graph display* • *Fixed trend arrow inconsistency with Dexcom app*
R1.9	• *Late advice now removes correction bolus. Updated text to encourage use after hypo treatment* • *Added revising when user insulin is less than recommended and user goes low* • *Fixed bug keeping new adaptation ICRs the same for new conditions*

- *Reduced ROC adjustment by 50%*
- *Added rejection for menstrual cycle and finger prick cases*
- *Fixed bug where user could bypass exercise selection if possible delayed advice detected*
- *Fixed bug where old ROC could possibly be used if finger prick BG given*
- *Fixed correction bolus adaptation case possibly causing later rejection conditions to not trigger*
- *Added settings option to disable menstrual adjustment for female participants*
- *Added revising for 0 insulin corrections*
- *Fixed bug causing rare double glucose entry*
- *Added safety condition saturating exercise to at least the rest ICR*
- *Fixed bug during revision where correction bolus cases didn't account for differing user insulin*

Table 4.20: Summary Log of the ABC4D Software Updates during the Clinical Trial

Versions of changes have been merged for simplicity (for example R1.9.3 and R1.9.4 both under R1.9). The updates considered at the time to impact the adaptation system are highlighted in green.

Abbreviations: insulin on board (IOB), insulin sensitivity factor (ISF), insulin to carbohydrate ratio (ICR), rate of change (ROC), blood glucose (BG).

4.9 Contribution of other team members to this chapter

I am very grateful to Ryan Armiger (engineer) who kindly undertook the following to assist my analysis:

- Cleaned and grouped the glucose data
- Extracted and calculated the number of hypo events for each participant within various time periods
- Extracted and calculated app usage data for each participant
- Extracted and calculated acceptance rates of all insulin doses by participant over various time periods

- Extracted adaptation metrics data for each participant enabling me to undertake analysis to compare the final to initial insulin to carbohydrate ratios
- Extracted the meal submission data from the last 2 weeks of the intervention and control periods to enable me to calculate the average insulin dose recommended and recorded as taken and the discrepancy in doses
- Extracted submission data across the entire study and settings data to enable me to summarise case parameter usage for each participant and analyse this data
- Extracted, filtered and analysed the data on app use of the note function (Table 4.18)
- Undertook the software updates during the clinical trial and compiled a table summarising the key changes which I have included in this chapter (Table 4.20)

Chapter 5: Discussion & Conclusion

Parts of this chapter have been accepted for publication in the Diabetes, Technology and Therapeutics journal (219).

Context

The majority of adults with T1D in England and Wales use MDI (82.3%) (16). It is widely recognised that intensive therapy delays the onset and slows the progression of micro- (32) and macrovascular (128) complications and the more frequently people adjust insulin doses for meals, the lower their HbA1c (129). Structured education programmes teach individuals how to interpret glucose readings, count carbohydrates and adjust their insulin doses to allow dietary and lifestyle flexibility. Insulin dose adjustments can be complex, involving the summation of meal insulin and correction dose insulin (130). A standard automated bolus calculator has been shown to reduce errors in insulin dose calculation (165) and improve treatment satisfaction (171, 174, 175). A standard bolus calculator has been associated with a greater HbA1c reduction compared to control but at the expense of increased hypoglycaemia (171), or has been associated with no significant difference in HbA1c change or hypoglycaemia frequency compared to control (173, 174). It lacks the ability to automatically change settings over time in response to changes in insulin sensitivity, such as with exercise (142), alcohol (147), stress (150) and menstrual cycle phases (151). Most individuals wait until review by a healthcare professional before making any changes to bolus calculator settings due to a lack of confidence, not knowing how to implement changes or the mis-conception that their settings never require changing (178). This can lead to infrequent reviews of settings and even in a clinic setting, the volume of data for a healthcare professional to interpret can be overwhelming, suggesting a

role for a decision support system to analyse the data and recommend therapeutic changes (157) and therefore allowing more time to focus on other aspects of diabetes holistic care.

The ABC4D is an adaptive decision support system for insulin bolus adjustment in MDI users, employing run-to-run and case-based reasoning techniques. The integrated system comprises a real-time insulin bolus calculator displayed as a smartphone application with real-time continuous glucose monitoring and a web-based clinician's platform. The ABC4D runs in adaptive bolus calculator mode (ABC4D; intervention) or non-adaptive bolus calculator mode (control). The main objective of my PhD project was to determine the safety and efficacy of the ABC4D compared to a standard non-adaptive bolus calculator in adults with T1D on MDI in an out of clinic setting. This was evaluated through a prospective 8 month randomised controlled cross-over study which included a 2-week run-in, 3-month intervention/control, 6-week wash-out and finally a 3-month control/intervention period.

Glycaemic outcomes compared to other studies

This study has demonstrated the safety of the ABC4D with no serious adverse events or episodes of severe hypoglycaemia. However, there were no significant differences in glycaemic outcomes between ABC4D and control. These results are in line with the majority of other single arm or randomised controlled studies which have shown no overall glycaemic benefit with DSS use for MDI users (198, 204, 205), CSII users (209) or both (201). These studies include those most comparable in design to ABC4D, as outpatient randomised controlled studies of either crossover (201) or parallel design (198, 209) using CGM, showing no glycaemic benefit compared to standard bolus calculator (201) or adjustments by a physician (198, 209). Bisio et al demonstrated an improvement in TIR 70-180mg/dL (+4.4%;

p = 0.003), reduction in TBR <60mg/dL (-0.7%; p = 0.049) and reduction in TAR > 250mg/dL (-3.3% ;p = 0.01) within the intervention group (DSS & RT-CGM) but there were no between group differences when compared to control (RT-CGM only) (207).

Studies which have demonstrated some improvement in glycaemic control with DSS use have not employed study designs or evaluated a study population comparable to the ABC4D study. The study designs employed have demonstrated a variety of limitations. Bode et al found a reduction in HbA1c in DSS users (10.2% baseline to 7.2% at 12 months, p < 0.001) but this was a retrospective observational quality improvement project with no control group and the majority (76%) had type 2 diabetes (206). Charpentier et al demonstrated an improvement in HbA1c with use of the Diabeo DSS over a 6 month period compared to control but no other glycaemic outcomes were reported and participants did not wear CGM (208). Pumptune was associated with greater percentage TIR 3.9-10.0mmol/L than physician settings (mean (SD) 64.3 (9.7)% versus 57.4 (11.4)%; p = 0.016) and lower percentage TAR >10mmol/L (26.9 (9.6)% versus 33.5 (13.6)%; p = 0.021); however only one set of recommendations were provided prior to the relatively short study period of 6.5 days (189). Singla et al conducted a single arm interventional study but without a standardised protocol for duration of intervention use and no baseline data reported for comparison (214). Studies by Zisser et al employing run-to-run control only tested the algorithm for a two week period (195, 196), with deliberate under-bolusing of insulin at the start and participants following a fixed diet (195) or usually consuming low carbohydrate diets with no information reported regarding the amount of carbohydrate consumed during the study period (196). Several randomised controlled cross over studies evaluating DSS use in controlled environments for short observation periods (duration of one day to 48 hours) have shown reduced percentage TBR (192) or specifically postprandial percentage TBR (210), reduced daytime glycaemic variability (192) and reduction

in glucose incremental area under the curve and incremental change in blood glucose concentration (193). Dassau et al (211) found a reduction in HbA1c and percentage TBR with use of a novel adaptive AP over a 12 week period, however it is not possible to differentiate the impact of the basal and bolus adaptations from the impact of the Zone MPC AP (212) and Health Monitoring System hypoglycaemia prediction algorithms (213) on glycaemic control, given the absence of a control group.

The ABC4D study found no difference in change in glycaemic outcomes between intervention and control for participants who accepted at least 90% of all recommendations during both the control and intervention phases. Whilst this was only a small number (n=9), these results are in contrast to other studies which have demonstrated glycaemic benefit associated with acceptance of recommendations (205) or active use of the DSS (207). However, the methodologies used in these sub-analyses were different to those which I used and may in part explain the differences in results observed. Castle et al (205) found that TIR improved by 6.3% in weeks when > 50% of recommendations by the DailyDose were accepted and followed from the prior week, compared to weeks when ≤ 50% recommendations were accepted from the prior week (95% CI 2.5-10.1%; p = 0.001). However, this post-hoc analysis focused on usage and glycaemic outcomes on a week-to-week basis, rather than the acceptance rate overall and comparison of glycaemic outcomes during the 2 weeks pre and last 2 weeks of treatment phase as in the ABC4D study. Additionally, "following" a recommendation was defined as dosing insulin within ± 25% of that recommended and using the bolus calculator for at least 75% of doses logged by the Bluetooth bolus insulin pen (205). We defined acceptance as following the recommendations exactly as they were and do not have data available on the proportion of bolus insulin doses participants actually used the ABC4D bolus calculator for and whether there was a correlation between this and glycaemic outcomes. However, we did show that there

was no change in glycaemic outcomes for participants with an average of at least 3 meal submissions per day throughout the control and intervention periods (n=19) and there was no correlation between the number of meal uses per week during the whole or last 2 weeks of the control/intervention periods and selected glycaemic outcomes. Bisio et al (207) found that "active users" of the inControl Advice app had a greater reduction in TBR at all thresholds. "Active users" were defined by a scoring system based on the frequency of requested exercise and bedtime advice, in addition to meal bolus calculator use (207) which was the focus in our post-hoc analysis for ABC4D. Additionally the acceptance rate of doses was not reported by Bisio et al (207).

Within group differences in the Control group

There was a significant within group reduction in percentage TBR <3.0 mmol/L and <2.8 mmol/L during the daytime and 24 hour period in the control group. The daytime decrease in percentage TBR <3.0 mmol/L was from a median of 0.3% (equivalent to 4.3 minutes) to 0.1% (equivalent to 1.4 minutes) and in percentage TBR <2.8 mmol/L from a median of 0.2% (2.9 minutes) to 0.0% (0 minutes). With low baseline values and small differences, this reduction may not be perceived as clinically significant for some individuals. These results are in contrast to those found with the inControl DSS (207), showing no within group changes for percentage TBR at various thresholds (<3.9 mmol/L (<70mg/dL); <3.3 mmol/L (<60mg/dL); <3.0 mmol/L (<54mg/dL); <2.8 mmol/L (<50mg/dL)) for the control group. The control group in this study used RT-CGM and were advised to inject insulin "as per their normal dosing regimen" with no clear information as to whether this could be a standard bolus calculator usually used or manual bolus calculations only. In contrast, the ABC4D control group used the non-adaptive bolus calculator with several features to reduce the risk of hypoglycaemia; insulin dose reductions

for planned or recent exercise, a negative ROC adjustment if the sensor glucose level was falling quickly and a delayed bolus option to prevent any correction dose or ROC adjustment. In addition, a safety pop up checked in cases of a rapidly increasing glucose level if the insulin was a delayed dose or the participant had recently treated an episode of hypoglycaemia and if a participant then selected "yes", then no correction dose insulin or additional insulin to adjust for the positive rate of change in glucose levels would be employed in the algorithm. Other randomised parallel or cross over studies have not reported within group changes for the control group at the hypoglycaemia thresholds of <3.0 mmol/L (<54mg/dL) and < 2.8 mmol/L (<50mg/dL) (198) or did not report within group differences (189, 192, 201, 209).

Challenges comparing results between DSS studies

Comparing results across DSS studies is challenging, given the variation in study designs and control group. Several studies were single arm pilot studies (195, 196, 204, 205, 211, 214) and one was a retrospective quality improvement project (206). The control arms of randomised controlled studies varied from CGM with telephone follow up (207), paper logbook with usual clinic follow up (208), insulin dose adjustments by a physician (189, 198, 235) or use of a standard bolus calculator (201, 210). To my knowledge, the PEPPER study (201) has been the only other outpatient study in MDI users which utilised a non-adaptive (standard) bolus calculator and RT-CGM in the control group.

Quality of life and ABC4D outcomes

The increase in DTSQ global total score was lower with ABC4D compared to control. There are several possible reasons for the smaller increase observed in satisfaction scores, including concerns regarding hypoglycaemia, not trusting the advice as much as control and perhaps

spending longer checking the dose recommendation. A lower percentage of all doses and meal doses were accepted by participants during the last 2 weeks of ABC4D use compared to control, with a greater reduction in dose from that which was recommended. This suggests perhaps that users were concerned about the risk of hypoglycaemia with ABC4D dose recommendations. However there were no between group or within group differences in change in the DTSQ perceived fear of hypoglycaemia score. The exercise adaptation recommended more insulin for lunch and dinner during the last 2 weeks of ABC4D use compared to at the start. The meal insulin doses with exercise throughout the control arm were equivalent to those at the start of the ABC4D arm, unless the participant had changed their lunch or dinner ICR during the run in or wash out period just prior to each treatment period. However the difference between the dose reported as taken and dose recommended with exercise did not vary significantly between the ABC4D and control arms during the last 2 weeks, suggesting that participants' concern regarding hypoglycaemia risk did not differ between ABC4D and control. A limitation of this observation is that the ICR changes were derived from 33 participants for each meal separately, whereas data from only 15 participants was used to calculate the average dose discrepancy across all meals with exercise, who had at least 1 meal submission with exercise during last 2 weeks of the control and intervention periods.

Another possibility for a lower increase in satisfaction scores is that users did not trust the ABC4D advice as much as the control advice. The control (non-adaptive bolus calculator) used the same settings throughout the 12 week period and therefore could be assumed to be more likely to recommend a dose similar to that which participants expected. However, the ABC4D acceptability questionnaire results demonstrated that there were no differences between ABC4D and control in terms of frequency of trusting the dose recommendation or checking

the dose breakdown prior to accepting or overriding it. Shepard et al held focus groups to explore participants' attitudes and concerns around using a personalised glucose advisory system, which revealed themes including challenges trusting the technology and apprehension regarding handing over control to an automated system (236). A main concern raised was the necessity of understanding how the advice was generated and some participants expressed a desire to view the algorithm or formula used (236). Although this personalised glucose advisory system was designed for pump users on CGM (236), the concerns raised may also be relevant to ABC4D. The Daily Dose DSS group interviewed participants who were not following recommendations and are incorporating these findings into a later iteration of their decision support app with a focus on improving interpretability and "explainability"(237, 238). Interpretability refers to an understanding of how an input leads to an output in an algorithm (237), for example how CGM/insulin dose data is used to generate the recommendation. "Explainability" can be seen as explaining in lay terms to the user why the system generated the particular recommendation (237). However, the DailyDose presented users with recommendations to approve (205) as compared to ABC4D in which the adaptations were performed automatically. Whilst ABC4D users were provided with a dose breakdose for each recommendation, perhaps also providing an explanation of why their ICR/ISF settings have changed may increase trust in the device and confidence in following the recommendations. There is a possibility in our study that participants spent longer checking the dose recommendation when using ABC4D compared to control, as the ICR/ISF were evolving, even though the data entry required and number of key strikes were the same for ABC4D and control. This may have potentially had an impact of satisfaction scores.

The Impact of the Covid Pandemic

During this study, the World Health Organisation declared the global Covid-19 pandemic on 11th March 2020, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-CoV2) (239). The UK government enforced a lockdown on 23rd March 2020 and ordered people to stay at home (240). The lockdown restrictions lead to unprecedented lifestyle changes including working from home and the closure of restaurants, pubs, gyms and swimming pools. At the start of the first lockdown, 18 participants had already been recruited, who then continued in the study with a switch from face to face to remote study visits. A further 19 participants were recruited remotely between October 2020 and February 2021, during which time there were two further national lockdowns in England and local lockdowns imposed based on a tier system (241). Data suggests that lockdown overall had a positive impact on glycaemic control for adults with T1D (242). A meta-analysis of 17 studies (n=3441 individuals with T1D) found that during the lockdown period, TIR 70-180mg/dL increased by 3.1% (95% CI 1.7 to 4.4%; p <0.0001) and TAR >180mg/dL and >250mg/dL decreased by 3.4% (-5.1 to -1.6%; p < 0.0001) and 2.0% (-2.5 to -1.4%; p < 0.0001) respectively (242). Possible explanations for these findings include more regular mealtimes during lockdown and changes in sleep patterns, even with reduced physical activity and more frequent snacking (243). These lifestyle changes during the lockdown restrictions may have affected participants' glycaemic control during the ABC4D study but the cross-over nature of the study may have reduced the potential impact.

The ABC4D study has demonstrated the feasibility of study adaptations to enable an interventional diabetes technology study to run entirely remotely. This was possible mainly

due to the ABC4D clinicians' web based platform, from which I was able to view participant's data and initiate or change settings, with fantastic support provided by the engineering team.

Strengths of this study

One of the main strengths of this study is the powered randomised controlled cross over study design with reasonably long control and intervention periods of 12 weeks each in free-living conditions in an outpatient setting. The cross over study design aimed to minimise the risk of a possible "Hawthorne" effect. It also aimed to reduce the risk of bias by introducing RT-CGM into a study for participants who had no previous experience of RT-CGM use, as it is widely recognised that RT-CGM use is associated with an improvement in glycaemic outcomes compared to SMBG (89-96) or isCGM (124-127). A novel feature of the ABC4D system is that adaptations are performed automatically on participants' smartphones and therefore enabling health care professionals to spend more time exploring other aspects of diabetes care during routine clinic appointments. In contrast, the majority of other DSS required recommendations to be approved by a healthcare professional prior to implementation (195, 196, 198, 201, 206, 211).

Limitations

Limitations of the study include only accounting for exercise and the time of the meal in the case base. There are many variables which impact glycaemic control, including those parameters which participants could select but did not change the dose recommendation. These were alcohol (147), stress (150), illness (149) and slow meal absorption (low GI foods) (135). Additionally selecting exercise led to the same dose reduction, regardless of the level of intensity and duration or whether it was recent or planned, aerobic or anaerobic or mixed

aerobic/anaerobic. This was a pragmatic decision to limit the number of potential cases to 6 and allow enough adaptations for each case to occur in order to assess an impact on glycaemic control. Focus groups run by Shepard et al around the use of a personalised glucose advisory system found that participants emphasised that the system needs to incorporate information on enough parameters which have an impact their glycaemic control and insulin requirements and if these are not accounted for, it could affect the perceived accuracy of advice generated (236). In line with this, participant feedback on the ABC4D acceptability questionnaire mostly requested further parameters to be added for insulin dose adjustment. Interestingly these suggested parameters were similar to those raised by participants in the focus group by Shepard et al (236), for example exercise duration and intensity and alcohol. However some participants in the ABC4D study indicated that they preferred minimal input data to avoid adding complexity and time burden. Pesl et al commented in reference to the pilot ABC4D study that the introduction of each extra parameter would increase the number of potential cases exponentially and consequently increase the convergence time and if requiring further manual user input, this could have a detrimental effect on usability (200). Böhm et al analysed real-world usage of a diabetes mobile health app (n= 9051), finding lower average user engagement over time if manual data entry was required for modules compared to automatic entry, despite higher initial uptake (244), suggesting possible user fatigue. Schwartz et al observed a high dropout rate in their study designed to build up the case base, which participants reported was partly due to the time burden required to enter life-event data (202). The amount of input data required was reduced in the follow up study, which led to a lower problem detection rate (2.6 problems per participant per week (203) compared to average 4.9 problems per participant per week in the first study (202)) but lower dropout rate (3 out 26 (203) compared to 8 out of 20 (202)).

Whilst a number of rejection criteria in our study were important to ensure the minimum postprandial glucose level for submissions accepted into the case base truly reflected the insulin dose taken and was not influenced by other variables, it restricted the number of adaptations in some cases, for example if participants ate frequently or gave correction doses frequently (unless particular criteria were satisfied).

Participants were not able to retrospectively edit or delete doses once accepted which could lead to an inaccurate IOB. This could also introduce error into the CBR algorithm, although using the median of 3 new proposed ICRs for each case was designed to reduce this potential risk.

Whilst a structured education refresher on carbohydrate counting was provided at randomisation, there was no formal assessment of carbohydrate counting confidence at screening or randomisation. If participants made frequent inconsistent significant errors in carbohydrate counting, this may have limited the impact of the intervention. However, consistent overestimation or underestimation of the carbohydrate content of meals would still allow the ABC4D system to learn and personalise recommendations. Participants were not completely blinded to their treatment allocation, as they could look at the insulin dose breakdown in the ABC4D app and work out if the ICR and ISF used to calculate the recommended dose were changing (intervention), or if the app continued to use the same settings entered at set up throughout the 12 week treatment period (control). Participants were asked to keep their basal insulin doses the same throughout the study unless there were safety issues i.e. problematic hypoglycaemia. This was designed to limit the impact of basal dose changes on glycaemic outcomes and therefore allow glycaemic outcomes to be attributed solely

to the bolus calculator. However not optimising the basal insulin during the run-in period may have limited the ability to optimise glycaemic outcomes with the bolus calculator.

There is a possibility of a carryover effect after the relatively short 6 week washout period, particularly for HbA1c at the start of the second treatment period given that it reflects glycaemic control over the last 8-12 weeks (31). A duration of 6 weeks was selected for the wash out period to balance the risk of a potential carry over effect against the extra time commitment for participants in an already relatively long study.

Potential modifications to the ABC4D system

There are several possible potential modifications to the ABC4D system which could improve usability and perceived value to some users, as suggested by participants in the ABC4D acceptability questionnaire or described with other DSSs. These include the integration of a nutritional database or fitness tracker, a hypoglycaemia treatment flag and bedtime dose adjustment, with further details provided below.

Suggestions from participants included the integration of a carbohydrate counter into the ABC4D app, using a food database and functionality to input the food weight or use a barcode scanner. This would be similar to the "T1-Life" smartphone app evaluated by Singla et al (214), which included a food database of popular Indian foods with their nutritional content. Participants entered their meal content and the app computed the macronutrient information automatically, with the calculated carbohydrate amount used in the real-time bolus calculator, in addition to the weekly ICR adjustments (214).

A number of participants wished to enter more information about the type of exercise they were about to do or had recently undertaken. Integration with a fitness tracker could simplify this and use of exercise recognition technology within the exercise tracker could automate this process. Some individuals may find further advice to manage their glucose levels around exercise useful, in addition to the bolus dose reductions as recommended by ABC4D. For example DailyDose (205) provides exercise advice according to consensus guidance (138) which also includes to consume additional carbohydrates. Alternatively an exercise risk warning system to predict hypoglycaemia risk at the start of exercise may be useful, with accompanying advice on treatments to reduce this risk such as carbohydrate consumption, as seen in the inControl Advice app (207).

Participant suggestions to improve hypoglycaemia recording using the ABC4D app included a specific hypoglycaemia treatment flag. A more advanced option would be using a personalised "carbohydrate correction factor" as employed in the PEPPER system (201), which was used to recommend an oral amount of carbohydrates in order to correct hypoglycaemia whilst reducing the risk of overcorrection and adapted over time. Participant feedback from ABC4D suggested a bedtime dose adjustment to reduce the risk of hypoglycaemia overnight. The bedtime ICR and ISF employed were the same as the dinnertime ICR. It could be argued that if individuals eat dinner early and regularly have a bedtime snack, there may be value to adding an additional bedtime case to the case base which would adapt independently to the dinner case. Or perhaps the integration of a bedtime button into the app would be useful, such as that employed in the inControl Advice app (207), which evaluated the risk of overnight hypoglycaemia and recommended a bedtime snack to mitigate this if necessary.

Whilst the aforementioned possible modifications based on other DSS apps have the potential to add value to app users, there is a paucity of published data on participant evaluation of app features, in terms of perceived usefulness and limitations or technical issues they experienced. Additional features add to app complexity which may be undesirable to some users who prefer simplicity. Involvement of users in the design and development of a mobile health app increases the likelihood of creating a product they engage with and this can translate into clinically significant outcomes. Cafezzo et al interviewed adolescents with T1D and their family caregivers to guide the design and development of a mobile health diabetes app, finding high satisfaction rates in the clinical pilot study and a significant increase in the frequency of daily SMBG from 2.4 to 3.6 tests per day ($p = 0.006$) (245).

Future potential of the ABC4D system

ABC4D did not adapt the basal doses in addition to bolus doses, in contrast with the majority of other DSS studies (189, 192, 198, 205, 206, 208, 209, 211, 214). Whilst it may then be challenging to ascertain whether it is the bolus adaptations, basal adaptations or both which are leading to an impact on glycaemic control, the addition of basal adaptations may be favourable in terms of glycaemic outcomes (246, 247). In silico evaluation of basal rate adaptation using run-to-run control for individuals using SAP has demonstrated an improvement in percentage TIR 70-180mg/dL and reduction in percentage TBR <70mg/dL for adults (246, 247) children (246) and adolescents (246).

Whilst the ABC4D system has been evaluated exclusively in MDI users, there is the potential for integration into insulin pumps. In addition to ICR adaptations, a potential area for further research would be adaptations of the combination bolus percentage split of up front/extended

bolus and the duration of the extended bolus for particular meal compositions, as demonstrated by Bell et al for a high fat, high protein meal (193). With increasing use of HCL systems, there is scope to introduce an adaptive bolus calculator to optimise postprandial glucose levels and reduce the need for basal rate adjustments to compensate for suboptimal postprandial glucose levels, which can take time to have an effect on glucose levels. Pump basal rate adaptations may also have a beneficial impact on glycaemia. Dassau et al have demonstrated promising results with the integration of bolus and basal adaptations into a HCL system (211).

Current DSS studies in the recruitment phase

There are several exciting DSS studies currently recruiting on the clinical trials registry (www.clinicaltrial.gov), three of which are by the DreamMed Advisor Pro group. The DreamMed Advisor Pro DSS- MDI algorithm is under evaluation in a single arm feasibility study (NCT04653961). Another single arm study is designed to assess the impact of use of the DreamMed Advisor Pro by healthcare providers at regular clinical visits or in between visits to adjust insulin settings for pump users on CGM including isCGM (NCT04271228). The Advisor Pro Direct study is a parallel randomised controlled study for CSII users on CGM, comparing pump setting adjustments by the Advisor Pro (intervention) to adjustments by the medical team (control) (recruitment target n=36) (NCT03774069). In both groups, participants download pump and CGM data at least every 4 weeks over the 3 month treatment period. The novel aspect here is that recommendations in the intervention group will be sent to the participants without review by a physician, unless glucose data meet certain safety criteria and in the control group, the onus is on the participants themselves to contact their medical team for assistance with insulin pump setting adjustments, unless there is a safety issue.

The “Adapting Diabetes Treatment Expert Systems to Patients in Type 1 Diabetes” (DSS-2) study (NCT04443153) is also recruiting and randomises participants into the escalation arm (sensor augmented mode to personalised feedback to DSS) or the de-escalation arm (interventions in the reverse order of the escalation arm). “Personalised feedback” only summarises the last week of data and the user decides on therapeutic changes. The primary outcome is glycaemic variability from CGM data and the study team are also aiming to describe the impact of psycho-behavioural factors on performance of the system, to facilitate system personalisation and automated adjustment of advice delivery in order to optimise glycaemia and reduce the psychological impact. This a very interesting and important area to explore, given that the clinical impact of a device is dependent upon an individual’s interaction with the artificial intelligence and their perceptions around device use influence their behaviour and uptake of the technology.

Conclusion

In conclusion, whilst the ABC4D system was safe, it was not associated with any changes in glycaemic outcomes compared to control. Participants accepted a lower percentage of doses in the last 2 weeks of ABC4D use compared to the non-adaptive bolus calculator (control), with a larger average reduction in dose compared to that which was recommended. This suggests that participants may not have felt comfortable taking these doses and this may have had an impact on effectiveness of the ABC4D, albeit possibly reduced the risk hypoglycaemia in some instances. Participant trust in a DSS and its usability influence their interactions with the DSS and potentially the clinical benefit they gain. The exploration of barriers in the uptake of and engagement with clinical DSS is an important area which requires further research. However, one of the main advantages with the ABC4D is the automatic adaptations performed locally on participants smartphones, without requiring approval by a health care professional prior to implementation. This could save time in routine clinic appointments and enable other aspects of diabetes care to be discussed in more detail. Future work could include further fine tuning of the algorithm, for example the sometimes large ICR/ISF mismatch which may have impacted participants' trust in the ABC4D advice if they did not feel confident taking the larger correction doses recommended. Participants' suggestions could be taken into consideration for future projects in our research team involving the design and development of mobile diabetes applications. The addition of basal dose adaptations and integration of the ABC4D algorithm into insulin pumps and HCL systems may be of benefit and would need evaluation in simulation and controlled studies.

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Appendix 1: Outputs

Peer reviewed publications (Original articles)

Unsworth R., Armiger R., Jugnee N., Thomas M., Herrero P., Georgiou P., Oliver N., Reddy M. Safety and Efficacy of an Adaptive Bolus Calculator for Type 1 Diabetes: a Randomised Controlled Crossover Study. Diabetes Technology and Therapeutics. Published Online ahead of print**:** 5 Apr 2023 https://doi.org/10.1089/dia.2022.0504

Unsworth, R.*, Wallace, S.*, Oliver, N.S., Yeung, S., Kshirsagar, A., Naidu, H., Kwong, R.M.W., Kumar, P. and Logan, K.M. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the UK. Diabetes Care. 2020; 43(11): pp.e170-e171.

Avari, P.*, **Unsworth, R**.*, Rilstone, S., Uduku, C., Logan, K.M., Hill, N.E., Godsland, I.F., Reddy, M. and Oliver, N. Improved glycaemia during the Covid-19 pandemic lockdown is sustained post-lockdown and during the "Eat Out to Help Out" Government Scheme, in adults with Type 1 diabetes in the United Kingdom. PloS one. 2021; 16 (7): p.e0254951.

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Poster presentations at conferences

Unsworth R., Armiger R., Herrero P., Georgiou P., Oliver N., Reddy M., 2023. Advanced Bolus Calculator for Type 1 Diabetes: Evaluation of case parameter and selection. Abstract ID 828. Poster at the Advanced Technologies and Treatments for Diabetes (ATTD) conference Berlin, Germany, 2023.

Mutiah A., **Unsworth R.,** Armiger R., Herrero P., Georgiou P., Oliver N., Reddy M. Predicting glucose dynamics as activity intensity increases in individuals with type 1 diabetes – a sub-analysis of the ABC4D study. Abstract ID 829. Poster at ATTD Berlin, Germany, 2023.

Hirani D., **Unsworth R.,** Mahmood A., Jones E., Begum F., Jairam C., Vieria S., Bound C., Menginstu Z., Jarvis S., Logan K., Oliver N., Watson M., Reddy M. A quality improvement project of a Young Adult Diabetes (YAD) service at a UK specialist centre. Poster at the European Society of Paediatric Endocrinology (ESPE) annual meeting online, 2021.

Unsworth, R., Godsland, I., Avari, P., Bound, C., Vieira, S., Logan, K., Oliver, N., Reddy, M. The effect of lockdown and easing of restrictions on glycaemia in children with Type 1 diabetes during the Covid-19 pandemic. Abstract ID 594. Poster at ATTD virtual conference, 2021.

Avari, P., **Unsworth, R**., Uduku, C., Rilstone, S., Hill, N., Godsland, I., Reddy, M., Oliver, N., Jun 2021. Improved glycaemia during the Covid-19 lockdown is sustained in adults with Type 1 diabetes. Abstract ID 643. Poster at ATTD virtual conference, 2021.

Avari, P., **Unsworth, R.,** Rilstone, S., Uduku, C., Logan, K., Hill, N., Godsland, I., Reddy, M., Oliver, N., Jun 2021. Higher levels of social deprivation associated with increased percentage time in range in people with Type 1 diabetes during Covid-19 lockdown. Abstract ID 360. Poster at ATTD virtual conference, 2021.

Unsworth, R., Vieira, S., Bound, C., Begum, F., Jairam, C., Silverstein, A., Hulme, S, Oliver, N., Watson, M., Reddy, M. The Young adult diabetes service: outcomes from focus groups with young people and the plan to implement their ideas. Abstract accepted for poster

presentation at the Diabetes UK Professionals Conference 2020, cancelled due to the Covid-19 pandemic.

Appendix 2: Adaptive Bolus Calculators Systematic Review

Manuscript

Adaptive Bolus Calculators for People with Type 1 Diabetes; a Systematic Review

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Short running title: Adaptive bolus calculators: a systematic review

Key words: adaptive bolus calculators, type 1 diabetes, hypoglycaemia, HbA1c, time in range

Manuscript word count: 3409 words

Abstract word count: 250 words

Figures and table count: 1 figure and 1 table

Supplementary material: 2 tables, search strategies & data extraction form

Abstract

Aims: Standard bolus calculators for people with type 1 diabetes (T1D) have shown variable outcomes with the main limitation that bolus advice does not automatically adapt in response to exogenous and endogenous factors, such as exercise, alcohol, stress, ambient temperature and hormonal cycle. We conducted a systematic review of studies assessing adaptive insulin bolus calculators.

Methods: Electronic databases (MEDLINE, EMBASE and WEB OF SCIENCE) were systematically searched from date of inception to 13th October 2022 for single arm or randomised controlled studies assessing adaptive bolus calculators only, in children or adults with T1D on multiple daily injections or insulin pumps with glycaemic outcomes reported. The Clinicaltrials.gov registry was searched for recently completed studies evaluating decision support in T1D. The quality of extracted studies was assessed using the Standard Quality Assessment criteria and the Cochrane Risk of Bias assessment tool.

Results: Six studies were identified. Extracted data were synthesised in a descriptive review due to heterogeneity. All the studies were small feasibility studies or not suitably powered and all were deemed high risk of performance and detection bias as they were unblinded. Overall these studies did not show a significant glycaemic improvement. Two studies demonstrated a reduction in postprandial time below range or incremental change in blood glucose concentration, however these were in controlled environments over a short duration.

Conclusion: There are limited clinical trials evaluating adaptive bolus calculators. Although results from small trials or in-silico data are promising, further studies are required to support personalised and adaptive management of T1D.

Introduction

The benefits of intensive insulin therapy in type 1 diabetes (T1D) have been well established[1,2]. The more frequently people adjust insulin doses for meals rather than using fixed doses, the lower their HbA1c[3]. However there are a number of barriers, including numeracy literacy[4,5], time and energy requirements and fear of hypoglycaemia[6]. Insulin dose adjustments can be complex and include the summation of meal insulin and correction dose insulin. The insulin bolus dose can be summarised by the following equation[7], which is employed in standard bolus calculator models.

$$\text{Bolus insulin} = \frac{\text{Meal insulin}}{\text{ICR}} + \frac{\text{Correction insulin}}{\text{current BG - target BG}} - \text{IOB}$$

$$\text{CHO} \qquad\qquad \text{ISF}$$

Abbreviations: blood glucose (BG), carbohydrate (CHO), insulin to carbohydrate ratio (ICR), insulin sensitivity factor (ISF), insulin on board (IOB)

Studies using a standard bolus calculator have shown no difference in HbA1c reduction compared to a control group using manual bolus calculations, when both groups have received additional education and enhanced care[8,9], with the exception of the ABACUS study[10] which demonstrated a greater reduction in HbA1c. There have been no between group differences observed in the number of hypoglycaemic events[8,9,11] or episodes of severe hypoglycaemia[9]. However, a standard bolus calculator has been found to reduce postprandial hypoglycaemia[8,12] and reduce dosing errors[13]. Bolus calculator use has not been shown to change fear of hypoglycaemia in the short term[9,11], but reduces fear over a longer period[12].

The main challenge with a standard bolus calculator, is that the ICR and ISF do not automatically adjust in response to changes in insulin sensitivity, such as influences from exercise[14], alcohol[15], menstrual cycle[16], ambient temperature[17] and stress[18]. The majority of individuals wait until routine appointments with a healthcare professional and do not change bolus calculator settings independently in between appointments because they lack confidence or don't know how to change the settings or don't realise that the settings might need changing[19]. Furthermore, during a routine clinic appointment, the volume of glucose data can be overwhelming for the healthcare professional to analyse[6].

Given the lack of ability to automatically adapt over time to respond to individual needs or changes in insulin sensitivity, it is hypothesised that an adaptive insulin bolus calculator will provide better glycaemic control than state-of-the-art standard bolus calculators. This is the first systematic review specifically looking at adaptive bolus calculators for individuals with T1D, including those using continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI).

Methods

Eligibility criteria

Studies meeting the following criteria were included: participants with type 1 diabetes, outpatient or inpatient studies, single arm studies using an adaptive bolus calculator/decision support/run-to-run control/case-based reasoning/another form of artificial intelligence to recommend changes in insulin bolus doses or randomised controlled studies comparing to a standard bolus calculator/manual bolus calculations and glycaemic outcomes reported. The following studies were excluded: participants with type 1 & 2 diabetes (unless data could be extracted for participants with type 1 diabetes separately), standard bolus calculator only, an adaptive simultaneous bolus and basal calculator, prediction of blood glucose only without decision support, in silico/simulation, decision support for diabetes diagnosis, description of the decision support method only or description of a future study.

This systematic review can be summarised by the following "PICOS" framework:

Participants**:** Adults/children with type 1 diabetes on multiple daily injections or pumps

Intervention**:** Adaptive bolus calculators which recommend changes in insulin bolus doses

Comparisons**:** Standard bolus calculator or manual bolus calculations or no comparator

Outcomes**:** Any published glycaemic outcome(s)

Study design**:** Single arm studies using an adaptive bolus calculator or any randomised controlled trials comparing an adaptive to standard bolus calculator or manual bolus calculations

Searching Strategy

The following bibliographic databases were searched from date of inception to 19th/20th April 2021; Medline, Embase and Web of Science. The searches were then re-run to cover publications dated 2021 (Medline and Embase) or 20th April 2021 (Web of Science) to 13th/14th October 2022 to ensure they were up to date. Search terms used are included in the supplementary material S1. Publications were restricted to those in the English language only and the following publication types were excluded: review articles, conference/meeting abstracts (unless full paper) and case reports. The clinicaltrials.gov registry was searched for recently completed trials using the terms "type 1 diabetes" and "decision support" on 23rd January 2023 after the initial database study selection.

Study Selection

Search results were imported into Co-vidence and duplicates removed. Two authors (RU, PA) independently scanned the titles and abstracts of records for relevance, retrieved the full reports and then independently evaluated the full text reports against the selection criteria. Any disagreements were resolved by consensus or discussion with the third reviewer (NO). One author (RU) scanned the titles of clinicaltrials.gov studies and if relevant, retrieved the study register entries, with exclusions verified by another author (PA). Pubmed searches were undertaken to match records to published studies.

Quality Assessment

Two reviewers (PA, RU) assessed the quality of the data using Standard Quality Assessment Criteria for evaluating primary research papers[20]. The two reviewers completed a standard

assessment form for assessing the quality of quantitative studies, consisting of 14 items scored on the degree to which the specific criteria are met ("yes" = 2, "partial" = 1, "no" = 0). If the items were not applicable to a particular study design, they were excluded from the summary score, which was calculated by the following equation (total score/(28-(number of items not applicable x 2)). In cases of a discrepancy in total score, a consensus was reached following discussion. Two reviewers (PA, RU) also independently completed the Cochrane Risk of Bias assessment tool[21] for extracted papers, with discrepancies resolved by discussion to reach a consensus. The risk of bias is assessed in 6 domains to be low/high/unclear[21].

Data Extraction & Synthesis

Data was extracted independently by one reviewer (RU) using a standardised form (Supplementary material 2) and checked by a second reviewer (PA). Extracted data included study population characteristics, insulin modality, glucose monitoring, study design, control/intervention details and glycaemic outcomes; these data were collated in a table. The effect measures of glycaemic outcomes were presented as they have been reported in the studies. Any disagreements were resolved by consensus or if necessary by a third reviewer (NO). Authors were contacted if additional information was required.

This systematic review has been reported according to the PRISMA 2020 guidance[22]. The review was not registered and a formal protocol was not prepared.

Results

Search Results

The initial and re-run database searches found 1920 records after duplicates were removed (figure 1). Following title and abstract screening, 1819 records were excluded as irrelevant. 101 reports were sought for retrieval and we were unable to retrieve one report, as not found online or in library archive. 100 reports were assessed for eligibility of which 94 were excluded, leaving 6 studies that fulfilled the eligibility criteria. The clinicaltrials.gov search found 40 records. Following screening of titles and the collated summary information, 27 study entry records were assessed for eligibility of which none fulfilled the criteria.

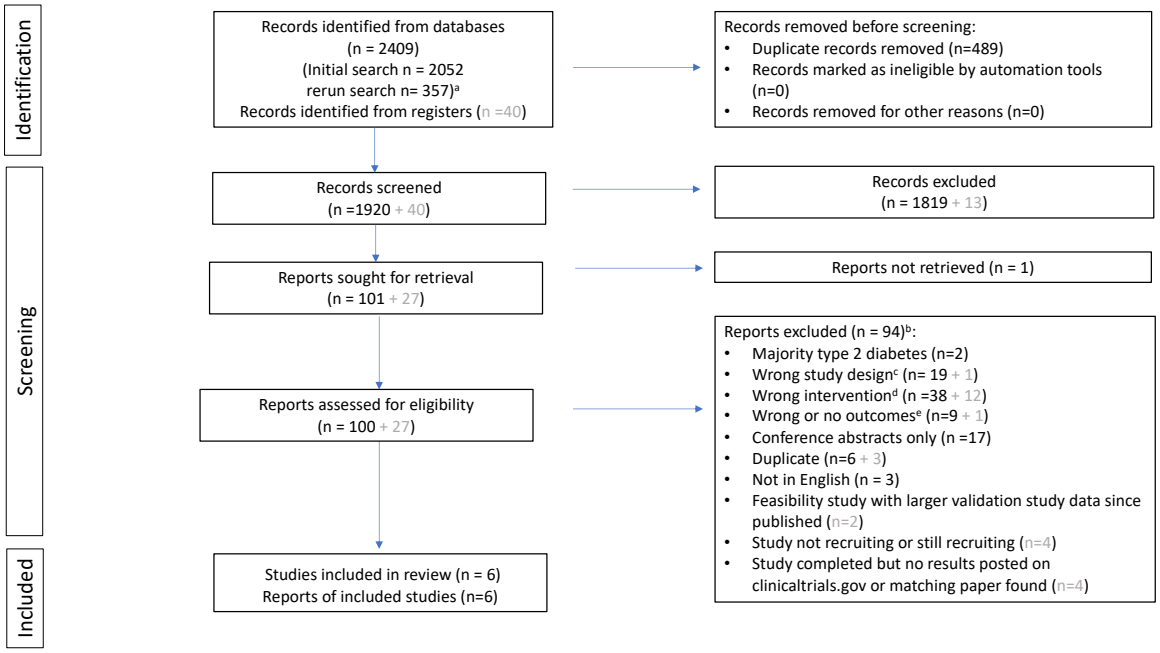


Figure 1: Study Flow Diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[22]

Pale grey text indicates records/study register entries from clinicaltrials.gov

[a] Initial search from date of inception to 19thApril 2021: Medline (n= 218), Embase (n=514). Initial search from date of inception to 20th April 20201: Web of science (n=1320).

Re-run search from 2021-13th April 2022: Medline (n=27), Embase (n=109) (Note overlap of initial and re-run searches for the period 1st January 2021 to 19th April 2021 as unable to use a specific start date in 2021 for the re-run search.) Re-run search from 20th April 2021 to 14th October 2022 Web of Science (n=221).

[b] Exclusion reason for a number of studies met > 1 criteria: they are only included under one category for simplicity

[c] Wrong study design includes full text papers describing system evaluation compared to medical experts using retrospective data (n=12), study in silico/simulation (n=1)

[d] Wrong intervention includes full text papers describing systems that predicts blood glucose only (n=2), adapts both bolus and basal insulin doses (n=14), standard bolus calculator only (n=1)

[e] Wrong or no outcomes includes a full text papers that provide a description of methods only (n=1)

There were a number of studies excluded with reasons listed in figure 1. The most common reason for exclusion was wrong intervention, particularly decision support systems that adapt both basal and bolus insulin doses, for example inControl Advice[23] NCT03093636, DailyDose[24] NCT0442864, the DiAS medical application platform NCT02558491 and the University of Virginia Decision Support System (UVA DSS)[25].

Study and patient characteristics

The 6 extracted studies included three single arm interventional studies[26-28] and three randomised controlled cross over studies[29-31] (table 1). Studies were in adults[26,27,29-31] with the exception of that by Singla et al in children/young people[28]. The proportion of female participants ranged from 10%[29] to 78% [27]. Studies included participants on MDI[26], CSII[27,29,31], both[30] or not stated[28]. Glucose monitoring was self-monitoring blood glucose (SMBG)[27], SMBG with blinded continuous glucose monitoring (CGM)[26,28], real-time continuous glucose monitoring (RT-CGM)[30,31] and venous blood samples analysed by the Yellow Springs Instrument (YSI) glucose analyser[29]. The algorithms used in the interventions employed case-based reasoning (CBR)[26,30], run-to-run control[27], a model-predictive bolus[29], reinforcement machine learning[28] and a model of glucose-insulin dynamics embedded into an optimally tuned

Kalman filter[31]. Control arms were standard bolus calculators[30,31], low fat low protein meal[29] or none[26-28]. Given the low number of extracted studies and their heterogenicity, the results were not synthesised and a descriptive review is provided instead.

Quality assessment

Exact agreement between the 2 reviewers for the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields Scale[20] was 33%. Discrepancies between the 2 reviewers were resolved through discussion, following which the agreement rate was 100%. The quality score assigned varied from 0.32 to 0.96 (Supplementary table 1).

Risk of Bias assessment

We conducted a risk of bias assessment for all studies (Supplementary table 2). All studies were deemed high risk of performance bias and detection bias as they were unblinded to participants and the research team. All studies were high risk of bias in terms of allocation concealment (except Fabris et al[31] where it was unclear as no details were provided). The reviewers scored Singla et al[28] high risk of bias across all domains.

Glycaemic outcomes

Time in range

Three studies reported percentage time at various glycaemic thresholds[26,28,30] (table 1). Avari et al[30] (n=54) found no difference in glycaemic outcomes with the Patient Empowerment through Predictive Personalised Decision Support (PEPPER) system compared to control,

including percentage time in range (%TIR) (3.9-10.0mmol/L (70-180mg/dL)) (median (IQR) 62.5 (52.1–67.8)% vs. 58.4 (49.6–64.3)%, p=0.27). Reddy et al (n=10) found no difference in %TIR between week 6 (final week) and week 1 of use of the Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) 60.9 (46.5-72.2)% vs 55.0 (50.1-56.7)%; p=0.9)[26]. Singla et al (n=5) reported that for the last week of usage (regardless of duration of intervention which was variable) TIR (70-180mg/dL) was 46.86% (range 39-66%)[28]. Whilst this seems lower than the other studies[26,30] and lower than consensus targets[32], there are no baseline data for comparison. The authors reported that in 3 children who used CGM in first week and last week, %TIR (70-180mg/dL) increased by an average of 16.67%[28] but with no measure of variability or statistical tests performed due to the small participant numbers. It is also not clear if the other 2 children did not wear CGM in week one and therefore were excluded from this analysis.

Hypoglycaemia

Avari et al[30] found no difference in percentage time below range (%TBR) at all thresholds with PEPPER compared to control, for example %TBR <3.9 mmol/L (<70mg/dL) (median (IQR) 2.2 (1.5-3.3)% vs 2.3 (1.1-6.4)%; p=0.64)). Reddy et al[26] showed no difference in % TBR with ABC4D at all thresholds in week 6 compared to week 1 (for example % TBR <3.9 mmol/L (median (IQR) 3.6 (0.6-9.8)% vs 5.0 (0.7-9.2)%; p = 0.7). Singla et al[28] reported that for the last week of app usage %TBR < 3.9 mmol/L was 8.83% (range 2.3-13.6%) but again with no comparison to baseline provided. Zisser et al[27] (n= 9) and Reddy et al[26] reported no episodes of severe hypoglycaemia. Avari et al[30] reported one episode of severe nocturnal hypoglycaemia in the control group, not thought to be related to the trial intervention. Fabris et al[31] (n=15) reported a "significant hypoglycaemia event" after discharge from the hotel admission, thought to be unrelated to their participation in the trial.

Hyperglycaemia

Avari et al[30] demonstrated no difference in percentage time above range (%TAR) between PEPPER and control (%TAR >10 mmol/L (> 180mg/dL) median (IQR) 35.2 (29.8 - 43.9)% vs 38.6 (30.6-48.0)%; p = 0.40) (%TAR >15 mmol/L (>270mg/dL) 4.5 (2.2-7.5)% vs 4.9 (2.7-9.4)%; p=0.50). Reddy et al[26] found no difference in %TAR between week 6 and 1 of ABC4D use (%TAR >10 mmol/L median (IQR) 36.9 (18.0-43.1)% vs 40.5 (26.3-47.3)%; p=0.5) (%TAR >15mmol/L median (IQR) 5.5 (2.1-19.3)% vs 9.3 (2.8-15.3)%; p=0.8). Singla et al[28] did not report %TAR results.

Postprandial glycaemic outcomes

Four studies reported glycaemic outcomes in the postprandial period[26,27,29,31] (table 1). Zisser et al[27] found that using the run-to-run control algorithm, the 1 hour postprandial blood glucose levels were mean (±SD) 104 ± 19mg/dl and 2 hour postprandial levels (96.5 ± 18 mg/dl) approached pre-prandial levels (90.1 ± 13 mg/dl). The differences in 1 hour postprandial blood glucose values between the period before convergence and maintenance period after convergence statistically significant for all 3 meals (p=0.013, p=0.023, p=0.0018 for breakfast, lunch & dinner respectively)[27]. At "convergence" was defined as the first day when target postprandial blood glucose values were reached[27]. Conversely Reddy et al[26] found no difference in postprandial glucose levels after 60 or 120 minutes (postprandial glucose at 60 minutes 8.6 (8.4-12.4) mmol/L week 6 versus 9.6 (8.1-10.3) mmol/L week 1; p=0.7) (postprandial glucose at 120 minutes 8.6 (7.6-10.9) mmol/L week 6 versus 9.3 (7.0-10.6) mmol/L week 1; p=0.5). Bell et al (n=10) compared an insulin bolus calculated using a model-predictive bolus algorithm to bolus calculated using the ICR delivered as a 50%/50% combination over 2 hours for a high fat high protein meal, finding that it decreased the

incremental area under the curve (iAUC) (27,092 ± 1,709 mg/dL.min to 11,712 ± 3,172 mg/dL.min; p=0.0013) and the incremental change in blood glucose concentration (73 ± 4mg/dL to 24 ± 11 mg/dL; p=0.001) [29].

Studies have demonstrated equivocal results in terms of postprandial hypoglycaemia [26,31]. An insulin-sensitivity informed bolus calculator compared to a standard bolus calculator was associated with a reduction in postprandial %TBR (<70mg/dL) (8.48 ± 1.88% vs 15.18 ± 12.21%; p=0.049) and postprandial low blood glucose index (LBGI) (2.02 ± 2.63 vs 3.31 ±2.45; p=0.006) [31]. Reddy et al found a trend towards a reduction in episodes of postprandial hypoglycaemia (<3.9 mmol/L) but this was not statistically significant (episodes within 6 hours postprandially 2 (0.5- 6.5) week 6 versus 4.5 (2.0-8.2) week 1; p=0.17)[26]. Avari et al[30] also found no statistical difference in number of postprandial hypoglycaemia episodes within 5 hours with PEPPER compared to control (median (IQR) 0.0 (0.0-1.0) vs 1.0 (0.0-1.0); p=0.75). Zisser et al[27] reported 12 hypoglycaemic measurements (<55mg/dL) over 230 meals, for which the mean glucose was 45.0 (± 5.0) mg/dL with no control group for comparison.

Glycaemic variability

Avari et al found no difference in glycaemic variability measures between the PEPPER and control groups[30]. including co-efficient of variation (CV) (median (IQR) 34,6 (31.6-38.0)% versus 35.6 (31.8-40.7)%; p=0.43), LBGI (0.6 (0.4-1.0) versus 0.6 (0.4-1.5); p=0.71) and high blood glucose index. (HBGI) (7.6 (6.2-9.8) versus 8.0 (6.3-10.5); p=0.40). Reddy et al demonstrated no difference in week 6 of ABC4D use compared to week one in terms of LBGI (2.8 (2.3-8.6) versus 4.3 (2.8-8.0); p =0.9) or HBGI (11.9 (5.8-17,7) versus 12.9 (8.6-14.6); p=0.7)[26].

Study	Avari 2021 [30]	Bell 2016[29]	Fabris 2020 [31]	Reddy 2016[26]	Singla 2021 [28]	Zisser 2009[27]
Participants (n)	54 (ITT)	10	15 (n=14 included for demographics & in analysis)	10	5	9 (n=8 completed)
Age of participants (years)	Median (IQR) 41.5 (32.3-49.8)	60.4 (± 11.3)	44.4 ± 12.7	47 ±17	Range 6-20	Range 21-65
Female n (%)	28 (51.8%)	1 (10%)	4 (28.6%)	Not reported	3 (60%)	7 (77.8%)
Average duration of T1DM (years)	Median (IQR) 21.0 (11.5-26.0)	Not reported	25.9 ±13.4	25 (16)	Range 1-16	14.8 ± 12.7
Baseline HbA1c % (mmol/mol)	Median (IQR) (7.7 (7.5-8.2)% (61.0 (58.0-66.1))	7.1 ±.0.8 (54 ± 7)	6.9 ± 0.9	8.4 ±1.5 (68 ±16)	Not reported	7.1 ±1.4
Insulin modality	MDI/CSII	CSII	CSII	MDI	Not reported	CSII
Group differences (if applicable)	No statistical difference between groups at baseline	Not reported	Not reported	N/A	n/a	
Length of follow up	8 months (4 week run in, 12 weeks in each treatment phase with 3-4 week washout between treatments)	3 - 6 study visits	4 week at home data collection then 2 x 24 hour admissions under semi-controlled conditions at local hotel	6 weeks	15-36 weeks (interparticipant variability)	6 weeks (testing of algorithm lasted 2 weeks)
Study Design	Open labelled multicentre randomised controlled cross over study	Randomised controlled cross over as to which meal ate first on first 2 admissions: LFLP or HFHP with identical insulin bolus using ICR (50%/50% combo bolus) then repeat HFHP meal on	Randomised controlled cross over study: control/experiment admissions at least 48 hours apart (washout). Both admissions employed standard BC for lunch pre-exercise then either standard BC (control)/IS informed	Single arm interventional	Pilot single arm open label	Open labelled, single arm study

		subsequent visits until set criteria met.	BC (intervention) for dinner post exercise			
Glucose monitoring	RT-CGM (Dexcom G5)	YSI glucose analyser from venous blood samples	RT-CGM (Dexcom G6)	SMBG + blinded CGM (ipro 2)	SMBG & Abbott Libre Pro (blinded CGM)	SMBG
Control (if applicable)	Standard bolus calculator (integrated into PEPPER handset)	LFLP meal	Standard bolus calculator in DiAS mobile platform, based on participants' usual treatment parameters, target glucose level 110mg/dL & 4h IOB curve for both meals.	None	None	None
Intervention	PEPPER: CBR algorithm adapts bolus doses & "carbohydrate correction factor" to correct hypoglycaemia Predictive glucose alerts Predictive low glucose suspend for CSII users Safety system provides personalised CHO recommendations to correct hypoglycaemia & dynamic insulin bolus constraint	HFHP meal repeated using MPB algorithm up to 4 times until set postprandial criteria met.	DiAS insulin-sensitivity (IS) informed BC for dinner, using same settings for ICR, ISF, IOB as during control (saturated to +/- 30% change from standard insulin dose & approved by physician) IS-informed BC: algorithm modulates the standard bolus with the ratio of IS calculated from 4/52 of historical data and real time assessment of IS at time of bolus (IS index).	ABC4D: At weekly study visits each case adaptation manually approved by study team before updating case base on iPhone (mean of ICR proposed if case adapted more than once) with safety constraints.	T1-Life": android mobile app Expert system: initial insulin prediction is rule based (500 & 1500 rule). ICR adjusted weekly based on CGM/SMBG data for each individual at each specific meal time. ISF modified on a case basis. Food database automated CHO counting.	Data analysed for previous 24 hours then suggested updated ICR for each meal for the next 24 hours (physician approved) or decrease CHO content
Method used for intervention	CBR	MPB algorithm	IS index uses CGM data, pump data and a model of glucose-insulin dynamics embedded into optimally tuned Kalman filter	CBR	Reinforcement machine learning algorithm	Run to run control algorithm
Glycaemic outcomes	No difference in glycaemic outcomes with PEPPER vs control, including % TBR at all thresholds, %TAR (>10.0 mmol/L	MPB decreased the glucose iAUC (27,092 ± 1,709 mg/dL min to 11,712 ± 3,172 mg/dL min; P= 0.0013) and the	IS-informed BC significantly reduced postprandial LBGI (2.02 ± 2.63 vs 3.31 ±2.45; p = 0.006)	Trend towards reduction in PP hypoglycaemia (<3.9 mmol/L) but not statistically significant; episodes within 4 hours PP : median (IQR) 3.5	Last week of usage TIR (70-180mg/dL) 46.86% (range 39-66%)	1 hour PP blood glucose level (104 ± 19mg/dl 2 hour PP levels (96.5 ± 18 mg/dl) approached pre-prandial levels (90.1 ± 13 mg/dl)

	and >15 mmol/L) and % TIR 3.9-10.0 mmol/L (70-180mg/dL) % TIR PEPPER versus control (median (IQR) 62.5 (52.1–67.8)% vs. 58.4 (49.6–64.3)%, p=0.27). No difference in glycaemic variability measures between PEPPER and control groups.	incremental change in blood glucose concentration (73 ± 4mg/dL to 24 ± 11 mg/dL; P = 0.001).	IS informed BC significantly reduced postprandial TBR <70mg/dL (8.48 ± 11.88% vs 15.18 ± 12.21%; p = 0.049) Trend of increased HBGI but not statistically significant (3.13 ± 4.42 vs 2.09 ± 3.48, p = 0.075) No change in %TAR >180 mg/dL or >250 mg/dL No change in % TIR 70-180mg/dL	(1.7-5.2) week 1 vs 1 (0-5) week 6, p = 0.2, within 6 hours PP 4.5 (2.0-8.2) week 1 vs 2 (0.5- 6.5) week 6 (p=0 .17) Trend suggesting reduction in %TBR (irrespective of cut offs used), increased TIR with no increase in % TAR (not statistically significant) No difference in PP glucose levels at 60 or 120 mins No difference in 2/4 hours postprandial AUC glucose No severe hypoglycaemia episodes during study	TBR (<70mg/dL) 8.83% (range 2.3-13.6%) In n=3 children who used CGMS in first week and last week, TIR (70-180mg/dL) increased by an average of 16.67%	12 hypoglycaemic measurements (<55mg/dL) over 230 meals (45± 5.0 mg/dL). No episodes of severe hypoglycaemia. “At convergence” is day when target postprandial blood glucose levels first reached. Differences in 1 hour PP blood glucose values between period before convergence and maintenance period after convergence statistically significant for all 3 meals (p = 0.013, p = 0.023, p = 0.0018 for breakfast, lunch & dinner respectively)

Figure 3: Characteristics of studies and participants

Values are mean ± SD unless otherwise stated

Abbreviations:, bolus calculator (BC), carbohydrate (CHO), case-based reasoning (CBR), continuous glucose monitoring (CGM), continuous subcutaneous insulin infusion (CSII), Diabetes assistant (DiAS), diabetes treatment satisfaction questionnaire (DTSQ), high blood glucose index (HBGI), high fat high protein (HFPF), incremental area under the curve (iAUC), insulin sensitivity (IS), insulin to carbohydrate ratio (ICR), intention-to-treat (ITT), low blood glucose index (LBGI), low fat low protein (LFLP), model predictive bolus (MPB), multiple daily injections (MDI), postprandial (PP), Patient empowerment through predictive personalised decision support (PEPPER), real-time continuous glucose monitoring (RT-CGM), self-monitoring blood glucose (SBMG), time above range (TAR), time below range (TBR), time in range (TIR), Yellow Springs Instrument (YSI).

Discussion

To date, there are limited trials on adaptive bolus calculators assessing clinical outcomes in people with T1D, with only 6 studies meeting our inclusion criteria. Of these, none of the studies demonstrated significant improvement in glycaemia compared to a standard bolus calculator, although they did demonstrate safety and feasibility. All the studies were small feasibility studies[26-29,31] with limited participant numbers, or not suitably powered[30]. Two studies demonstrated a reduction in postprandial time below range[31] or incremental change in blood glucose concentration[29], however these were in controlled environments over a short duration.

A limitation of this systematic review is the exclusion of studies that adapted both the basal and bolus doses. We excluded these due to the difficulty of evaluating whether the net benefit is due to basal or bolus adaptation, or both. However, they are important in demonstrating proof-of-concept. Additionally, it is useful to assess the impact of bolus adaptations specifically in people on MDI, which remains the majority of adults in England and Wales (82.3%)[33]. Studies evaluating DSS that recommend adjustments to basal and bolus insulin in MDI users alongside intermittently scanned continuous glucose monitoring (isCGM) or rtCGM have shown no glycaemic benefit, either as a single arm [24] or compared to control[23,34]. However data suggested that accepting recommendations was associated with an improvement in TIR[24] and active use of the inControl Advice app was associated with a reduction in hypoglycaemia[23]. Breton et al[25] 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[25]. The UVA DSS significantly reduced

hypoglycaemia without increasing the mean rtCGM values, as well as reduced glucose variability[25].

The first automated decision support system approved by the FDA in June 2018 is the DreaMed Advisor Pro (DreaMed Diabetes Ltd, Petah Tikva, Israel), 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). The Endo.Digital DSS (version 2, DreaMed Diabetes Ltd, Petah Tikva, Israel) is similar for MDI users. Whilst the majority of studies by Nimri *et al* have been non-interventional and compared insulin dose adjustment by these DSS to physicians using retrospective data[35-37], one study evaluated real-time remote insulin adjustments by the DreamMed Advisor Pro to physicians every 3 weeks over a 6 month period, demonstrating similar levels of glycaemic control in children and adolescents on a pump and CGM[38]. However, the limitation of this system is the intention to aid clinicians with therapy adjustments, as opposed to the individual directly. Providing support to the user directly, not only facilitates more patient centred care, but empowers users in real-time. Furthermore, meta-analyses suggest that providing recommendations to both users and providers improves adherence and is more effective than providing decision support to providers only[39].

Dassau et al[40] investigated the use of decision support to optimise parameters within a hybrid closed-loop. Thirty adults with T1D participated in a single arm 12- week feasibility study, using model-predictive control, a control engineering algorithm, combined with the Health Monitoring System hypoglycaemia prediction algorithm[40]. Compared with run-in on sensor augmented pump therapy, %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)[40]. 10% of adaptation recommendations were manually overridden. Larger, randomised control trials are required to evaluate overall efficacy.

Finally, there are many promising studies conducted in-silico. Cappon et al[41] uses a neural network approach to optimise and personalise meal bolus calculation using rtCGM data. The system was testing in-silico using 100 meals, with its use significantly decreasing the blood glucose risk index after meals[41]. 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[42]. 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[42].

Although there are a significant number of in-silico studies, these algorithms need to be used by people with T1D to assess the associated risk of hypoglycaemia. Within experimental fully closed-loop systems, there is still a 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[43]. On the other hand, if the controller is not aggressive enough to an administered meal, there is a higher risk of insulin underdosing[44]. Similar principles are likely to apply in bolus calculators for differing algorithms.

Overall, the reasons for the limited clinical research in this field are unclear, but may 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, a challenging regulatory environment for approval, and the lack of connected insulin pens to fully support insulin inputs into an automated system[45]. We propose with the growing use of the hybrid closed loops, there is an ever-increasing need for adaptive bolus calculators to support a fully automated closed loop.

Conclusion

In summary, the number of clinical trials facilitating adaptive bolus calculators is limited. Furthermore, clinical studies in humans and outcomes involving AI for automated real-time adaptation to people with T1D remain in the primitive stage. There are limited large, and suitably powered, 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 and adaptive management of T1D.

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Systematic Review Supplementary Material

Paper	Quality Score
Avari 2021 [30]	0.96
Bell 2006 [29]	0.58
Fabris 2020 [31]	0.79
Reddy 2016 [26]	0.82
Singla 2022 [28]	0.32
Zisser 2009 [27]	0.64

Supplementary Table 1: Authors' Overall Consensus Quality Score on a Variety of Fields Scale (maximum score 1.00) [20]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants & personnel for all outcomes (performance bias)	Blinding of outcome assessors for all outcomes (detection bias)	Incomplete data for all outcomes (attrition bias)	Selective outcome reporting (reporting bias)	Other sources of bias
Avari 2021 [30]	Low	High	High	High	Low	Low	Low
Bell 2006 [29]	High	High	High	High	Low	High	Low
Fabris 2020 [31]	Unclear	Unclear	High	High	Low	Low	Low
Reddy 2016 [26]	High	High	High	High	Low	Low	Low
Singla 2022 [28]	High	High	High	High	High	High	High
Zisser 2009 [27]	High	High	High	High	Low	High	Low

Supplementary Table 2: Cochrane risk of bias assessment [21]

Paper	
Population	
Inclusion criteria	
Exclusion criteria	
Baseline characteristics	
Number of participants	
Age of participants	
Female (%)	
Average duration of T1DM	
Baseline HbA1c	
Insulin modality (MDI/CSII)	
Group differences (if applicable)	
Study design	
Length of follow up	
Study Design	
Glucose monitoring	
Intervention	
Control (if applicable)	
Intervention	
Outcomes	
Glycaemic outcomes	

Supplementary Table 3: Data Extraction Form

Search Strategies

a) Date of inception to 19th /20th April 2021

i) Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to April 19, 2021>

Search Strategy:

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1 Diabetes Mellitus, Type 1/ (77466)

2 insulin dependent.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (29192)

3 (T1DM or IDDM or T1D).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (19386)

4 (diabet* adj2 type 1).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (92867)

5 (diabet* adj2 type one).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (71)

6 1 or 2 or 3 or 4 or 5 (109529)

7 (run to run or machine learning or automat* or personali?ed or adaptive or artificial intelligence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (536864)

8 case base? reasoning.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept

word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (333)

9 Neural Networks, Computer/ (29176)

10 Deep Learning/ (4864)

11 exp Algorithms/ (343472)

12 run-to-run.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1082)

13 7 or 8 or 9 or 10 or 11 or 12 (790470)

14 Decision Support Systems, Clinical/ (8390)

15 (decision support or diabet* support or bolus calculator* or bolus advisor* or expert system* or advisor* system*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (44842)

16 ((app*1 or smartphone or mobile phone or mobilephone) adj7 bolus).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15)

17 (prandial insulin dos* or prandial-insulin dos* or meal related insulin dos* or meal-related insulin dos* or meal-time insulin dos*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (80)

18 (meal* adj2 insulin dos*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (95)

19 insulin dos* recommend*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept

word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23)

20 insulin recommend*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (22)

21 14 or 15 or 16 or 17 or 18 or 19 or 20 (45007)

22 6 and 13 and 21 (218)

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ii. Embase

Database: Embase Classic+Embase <1947 to 2021 April 19>

Search Strategy:

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1 insulin dependent.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (379768)

2 (T1DM or IDDM or T1D).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (33652)

3 (diabet* adj2 type 1).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (77238)

4 (diabet* adj2 type one).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (187)

5 exp insulin dependent diabetes mellitus/ (122005)

6 1 or 2 or 3 or 4 or 5 (393936)

7 exp algorithm/ (429949)

8 artificial neural network/ (38451)

9 machine learning/ (37316)

10 exp artificial intelligence/ (46795)

11 (run to run or run-to-run or machine learning or automat* or personali?ed or adaptive or artificial intelligence).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (817981)

12 case base? reasoning.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (455)

13 7 or 8 or 9 or 10 or 11 or 12 (1164494)

14 (meal* adj2 insulin dos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (209)

15 (prandial-insulin dos* or meal-time insulin dos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (174)

16 prandial insulin dos*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (167)

17 (meal related insulin dos* or meal-related insulin dos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (10)

18 (decision support or diabet* support or bolus calculator* or bolus advisor* or expert system* or advisor* system*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (43038)

19 ((app*1 or smartphone or mobile phone or mobilephone) adj7 bolus).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (31)

20 exp decision support system/ (27557)

21 insulin recommend*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (43)

22 insulin dos* recommend*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (43)

23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (43639)

24 6 and 13 and 23 (514)

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iii. **Web of Science (**Unable to include the search strategy here as it was saved as screenshots and is 42.3MB in size. However this search strategy was identical to the re-run search on 14th October 2022)

b) Re-run April 2021 to 13th/14th October 2022

i. Medline

Database: Ovid MEDLINE(R) ALL <1946 to October 13, 2022>

Search Strategy:

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1 Diabetes Mellitus, Type 1/ (83764)

2 insulin dependent.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (29550)

3 (T1DM or IDDM or T1D).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (21979)

4 (diabet* adj2 type 1).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (99570)

5 (diabet* adj2 type one).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (97)

6 1 or 2 or 3 or 4 or 5 (116587)

7 (run to run or machine learning or automat* or personali?ed or adaptive or artificial intelligence).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (641662)

8 case base? reasoning.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (358)

9 Neural Networks, Computer/ (43302)

10 Deep Learning/ (13041)

11 exp Algorithms/ (410010)

12 run-to-run.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1162)

13 7 or 8 or 9 or 10 or 11 or 12 (927786)

14 Decision Support Systems, Clinical/ (9210)

15 (decision support or diabet* support or bolus calculator* or bolus advisor* or expert system* or advisor* system*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (49630)

16 ((app*1 or smartphone or mobile phone or mobilephone) adj7 bolus).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17)

17 (prandial insulin dos* or prandial-insulin dos* or meal related insulin dos* or meal-related insulin dos* or meal-time insulin dos*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (90)

18 (meal* adj2 insulin dos*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (104)

19 insulin dos* recommend*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (28)

20 insulin recommend*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (24)

21 14 or 15 or 16 or 17 or 18 or 19 or 20 (49820)

22 6 and 13 and 21 (243)

23 limit 22 to yr="2021 -Current" (27)

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ii) Embase

Database: Embase Classic+Embase <1947 to 2022 October 13>

Search Strategy:

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1 insulin dependent.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (423680)

2 (T1DM or IDDM or T1D).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (38081)

3 (diabet* adj2 type 1).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (85636)

4 (diabet* adj2 type one).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (226)

5 exp insulin dependent diabetes mellitus/ (134277)

6 1 or 2 or 3 or 4 or 5 (439136)

7 exp algorithm/ (520501)

8 artificial neural network/ (45229)

9 machine learning/ (71041)

10 exp artificial intelligence/ (67637)

11 (run to run or run-to-run or machine learning or automat* or personali?ed or adaptive or artificial intelligence).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (963981)

12 case base? reasoning.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (490)

13 7 or 8 or 9 or 10 or 11 or 12 (1368707)

14 (meal* adj2 insulin dos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (229)

15 (prandial-insulin dos* or meal-time insulin dos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (186)

16 prandial insulin dos*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (180)

17 (meal related insulin dos* or meal-related insulin dos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (11)

18 (decision support or diabet* support or bolus calculator* or bolus advisor* or expert system* or advisor* system*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (48248)

19 ((app*1 or smartphone or mobile phone or mobilephone) adj7 bolus).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (41)

20 exp decision support system/ (31800)

21 insulin recommend*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (46)

22 insulin dos* recommend*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (49)

23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (49771)

24 6 and 13 and 23 (619)

25 limit 24 to yr="2021 -Current" (109)

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iii) Web of Science

Web of Science Search Strategy (v0.1)

Database: All Databases

Entitlements:

- WOS: 1970 to 2022
- BCI: 1969 to 2008
- CABI: 1973 to 2022
- KJD: 1980 to 2022
- MEDLINE: 1950 to 2022
- SCIELO: 2002 to 2022

Searches:

1: TS = insulin dependent Date run: Fri Oct 14 2022 19:53:24 GMT+0100 (British Summer Time) Results: 276415

2: TS= (T1DM or IDDM or T1D) Date run: Fri Oct 14 2022 20:16:09 GMT+0100 (British Summer Time) Results: 35641

3: TS= (diabet* NEAR/2 "type 1") Date run: Fri Oct 14 2022 20:16:16 GMT+0100 (British Summer Time) Results: 138329

4: TS= (diabet* NEAR/2 "type one") Date run: Fri Oct 14 2022 20:16:25 GMT+0100 (British Summer Time) Results: 183

5: #4 OR #3 OR #2 OR #1 Date run: Fri Oct 14 2022 20:16:34 GMT+0100 (British Summer Time) Results: 357372

6: TS= "run to run" Date run: Fri Oct 14 2022 20:16:42 GMT+0100 (British Summer Time) Results: 2075

7: TS= "run-to-run" Date run: Fri Oct 14 2022 20:16:48 GMT+0100 (British Summer Time) Results: 2075

8: TS= (machine learning or automat* or personali?ed or adaptive or artificial intelligence) Date run: Fri Oct 14 2022 20:16:57 GMT+0100 (British Summer Time) Results: 3072741

9: TS= case base? reasoning Date run: Fri Oct 14 2022 20:17:08 GMT+0100 (British Summer Time) Results: 66545

10: TS= neural network Date run: Fri Oct 14 2022 20:17:16 GMT+0100 (British Summer Time) Results: 724377

11: TS= ("machine learning" or "deep learning") Date run: Fri Oct 14 2022 20:17:24 GMT+0100 (British Summer Time) Results: 478168

12: TS= algorithm* Date run: Fri Oct 14 2022 20:17:32 GMT+0100 (British Summer Time) Results: 2864914

13: #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 Date run: Fri Oct 14 2022 20:17:40 GMT+0100 (British Summer Time) Results: 5551880

14: TS= (decision support or diabet* support or bolus calculator* or bolus advisor* or expert system* or advisor* system*) Date run: Fri Oct 14 2022 20:17:48 GMT+0100 (British Summer Time) Results: 732807

15: TS= (smartphone NEAR/7 bolus) Date run: Fri Oct 14 2022 20:17:57 GMT+0100 (British Summer Time) Results: 7

16: TS= (mobilephone NEAR/7 bolus) Date run: Fri Oct 14 2022 20:18:03 GMT+0100 (British Summer Time) Results: 0

17: TS= (mobile phone NEAR/7 bolus) Date run: Fri Oct 14 2022 20:18:12 GMT+0100 (British Summer Time) Results: 1

18: TS= prandial insulin dos* Date run: Fri Oct 14 2022 20:18:22 GMT+0100 (British Summer Time) Results: 1764

19: TS= prandial-insulin dos* Date run: Fri Oct 14 2022 20:18:28 GMT+0100 (British Summer Time) Results: 568

20: TS= meal related insulin dos* Date run: Fri Oct 14 2022 20:18:49 GMT+0100 (British Summer Time) Results: 1935

21: TS= meal-related insulin dos* Date run: Fri Oct 14 2022 20:18:56 GMT+0100 (British Summer Time) Results: 140

22: TS= meal-time insulin dos* Date run: Fri Oct 14 2022 20:19:04 GMT+0100 (British Summer Time) Results: 184

23: TS= (meal* NEAR/2 insulin dos*) Date run: Fri Oct 14 2022 20:19:11 GMT+0100 (British Summer Time) Results: 174

24: TS= "insulin dos* recommend*" Date run: Fri Oct 14 2022 20:19:22 GMT+0100 (British Summer Time) Results: 33

25: TS= "insulin recommend*" Date run: Fri Oct 14 2022 20:19:32 GMT+0100 (British Summer Time) Results: 34

26: TS= (app* NEAR/7 bolus) Date run: Fri Oct 14 2022 20:19:45 GMT+0100 (British Summer Time) Results: 2956

27: #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 Date run: Fri Oct 14 2022 20:19:53 GMT+0100 (British Summer Time) Results: 739183

28: #27 AND #13 AND #5 Date run: Fri Oct 14 2022 20:20:03 GMT+0100 (British Summer Time) Results: 1605

29: #27 AND #13 AND #5 Timespan: 2021-04-20 to 2022-10-14 Date run: Fri Oct 14 2022 20:20:44 GMT+0100 (British Summer Time) Results: 221

ClinicalTrials.gov Search Results 01/23/2023

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Assessment of a Decision Support Tool in Participants With Type 1 Diabetes	Completed	Has Results	•Type 1 Diabetes	•Device: DailyDose Decision Support	•Oregon Health and Science University, Portland, Oregon, United States
2	Feasibility of a Decision Support System to Reduce Glucose Variability in Subject With T1DM	Completed	No Results Available	•Type 1 Diabetes Mellitus	•Device: Decision Support System	•University of Virginia Center for Diabetes Technology, Charlottesville, Virginia, United States
3	Efficacy of inControl Advice: A Decision Support System (DSS) for Diabetes	Completed	Has Results	•Type1 Diabetes Mellitus	•Device: Continuous Glucose Monitor (CGM)+Decision Support System (DSS) •Other: Continuous Glucose Monitor (CGM) alone	•Stanford University, Stanford, California, United States •Icahn School of Medicine at Mt. Sinai, New York, New York, United States •University of Virginia, Charlottesville, Virginia, United States
4	Insulin Pump-RT Advisor (IPRA©): a Decision Support Software for Diabetic Patients Treated by Insulin Pump and Using Continuous Glucose Monitoring. Experimental Study. Evaluation by an Expert Patient Panel.	Completed	No Results Available	•Type 1 Diabetes	•Other: A decision support software •Other: Insulin Pump •Other: Continuous glucose monitoring	•Service d'Endocrinologie-Diabétologie - CHU de Rennes - Hôpital Sud, Rennes, France
5	Patient Empowerment Through Predictive Personalised Decision Support	Completed	No Results Available	•Type1 Diabetes Mellitus	•Device: PEPPER	•Imperial College Clinical Research Facility, London, United Kingdom
6	Study to Assess the Metabolic Impact of IRTA© and Patients Satisfaction in Type 1 Diabetic Patients, Treated by Either Insulin Pump or Multiple Daily Insulin Injections, and Using Freestyle Libre®, a Real-time Continuous Glucose Monitoring	Completed	No Results Available	•Type 1 Diabetes	•Other: A decision support software	•CHU de Rennes, Rennes, France
7	Evaluation of a Decision Support System for People With Diabetes Who Use Multiple Daily Insulin Injections- Feasibility Study	Recruiting	No Results Available	•Type1d|abetes	•Device: DreaMed Advisor Pro DSS-MDI algorithm	•schneider children medical center of Israel, Petach Tikva, Israel •Rabin Medical Center- Belinson, Petah-Tikva, Israel
8	Patient-Centered Decision Support to Improve Diabetes Management in Pre-Teens and Adolescents With Type 1 Diabetes	Completed	No Results Available	•Diabetes Mellitus	•Other: Arm 1	•Riley Hospital for Children, Indianapolis, Indiana, United States
9	CloudConnect: Predictive And Retrospective Clinical Decision Support For Chronic Disease Management	Completed	No Results Available	•Type 1 Diabetes Mellitus	•Other: CloudConnect Report •Other: Will not receive a CloudConnect Report	•University of Virginia Center for Diabetes Technology, Charlottesville, Virginia, United States
10	Patient Empowerment Through Predictive Personalised Decision Support(PEPPER)-Validation Study.	Completed	No Results Available	•Diabetes Mellitus, Type 1	•Device: PEPPER system	•Institut d'Investigació Biomèdica de Girona (IDIBGI), Girona, Spain
11	Patient Empowerment Through Predictive Personalised Decision Support (PEPPER)	Completed	No Results Available	•Diabetes Mellitus, Type 1	•Device: PEPPER system	•Institut d'Investigació Biomèdica de Girona (IDIBGI), Girona, Spain
12	Evaluation of Physician-based Decision Support	Completed	Has Results	•Type 1 Diabetes Mellitus •MDI •CGM •Exercise	•Device: Dexcom G6 CGM	•Oregon Health and Science University, Portland, Oregon, United States
13	Use of Insulin Adjustment Device DreaMed Advisor Pro During Routine Clinical Use for Subjects With Diabetes Type 1	Recruiting	No Results Available	•Type 1 Diabetes	•Device: DreaMed Advisor Pro	•Schnider Children's Medical Center, Petach-Tikva, Israel
14	Decision Coaching for Youth and Parents Considering Insulin Delivery Methods for Type 1 Diabetes	Completed	No Results Available	•Type 1 Diabetes Mellitus	•Behavioral: Decision coaching with a patient decision aid	•Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada
15	The Expert System VoiceDiab in Children With Diabetes	Unknown status	No Results Available	•Type 1 Diabetes Mellitus With Hyperglycemia •Type 1 Diabetes Mellitus With Hypoglycaemia	•Device: VoiceDiab expert system	•Ewa Pankowska, Warsaw, Poland
16	Exercise Activity-Based Bolus Decisions in Type 1 Diabetes	Completed	No Results Available	•Type 1 Diabetes Mellitus	•Other: Activity on Board •Other: Usual Diabetes Care	•University of Virginia Center for Diabetes Technology, Charlottesville, Virginia, United States

	Title	Status	Study Results	Conditions	Interventions	Locations
17	Adapting Diabetes Treatment Expert Systems to Patient in Type 1 Diabetes	Recruiting	No Results Available	•Diabetes Mellitus, Type 1	•Device: Personalized Feedback •Device: Decision Support System •Device: Sensor Augmented Mode	•University of Virginia Center for Diabetes Technology, Charlottesville, Virginia, United States
18	Clinical Assessment of a Novel Advanced Bolus Calculator for Type 1 Diabetes 5	Unknown status	No Results Available	•Type 1 Diabetes Mellitus	•Device: ABC4D •Device: Standard Bolus Calculator	•Imperial College Clinical Research Facility, London, United Kingdom
19	Web-Based Simulation Tool For Self-Management Support In Type 1 Diabetes Mellitus	Completed	No Results Available	•Type 1 Diabetes	•Other: Web-based Simulation Tool	•University of Virginia - Center for Diabetes Technology, Charlottesville, Virginia, United States
20	Technological Advances in Glucose Management in Older Adults	Active, not recruiting	No Results Available	•Type 1 Diabetes Mellitus •Older Adults •Hypoglycemia	•Other: eCGM (enhanced CGM)	•Joslin Diabetes Center, Boston, Massachusetts, United States
21	Adaptive, Real-time, Intelligent System to Enhance Self-care of Chronic Disease	Completed	Has Results	•Diabetes Mellitus, Type 1	•Device: ARISES	•Imperial College Clinical Research Facility, London, United Kingdom
22	The Advisor Pro Direct Study	Recruiting	No Results Available	•Type 1 Diabetes Mellitus	•Device: DreaMed Advisor Pro •Other: Medical guided recommendation	•Schnider Children's medical center, Petach Tikva, Israel
23	Personalized Automated Determination of Insulin Pump Setting for Subjects With Type 1 Diabetes Switching From MDI to Pump Therapy and Vice Versa- Safety and Efficacy Feasibility Study	Completed	No Results Available	•Type1diabetes	•Device: MD-Logic Switch Advisor	•Schnider children's medical center, Petach-Tikva, Israel
24	Closed Loop Insulin Therapy in Type 1 Diabetics Based on Blood Microdialysis, Online Sensors and an eMPC Algorithm	Completed	No Results Available	•Type 1 Diabetes		•Medical University Graz - Clinical Research Center, Graz, Styria, Austria
25	Virtual Diabetes Specialty Clinic: A Study Evaluating Remote Initiation of Continuous Glucose Monitoring	Active, not recruiting	No Results Available	•Type 1 Diabetes •Type 2 Diabetes	•Other: Virtual Clinic	•Jaeb Center for Health Research, Tampa, Florida, United States
26	The Bio-Inspired Artificial Pancreas for the Home	Terminated	No Results Available	•Diabetes Mellitus, Type 1	•Device: BiAP •Device: ABC4D	•Imperial College Clinical Research Facility, London, United Kingdom
27	Study of Intensive, Home-Based Family Therapy to Improve Illness Management in Youth With Diabetes	Completed	No Results Available	•Diabetes Mellitus, Insulin Dependent	•Behavioral: Intensive Home-Based Family Therapy •Behavioral: Supportive Telephone Calls	•Children's Hospital of Michigan, Detroit, Michigan, United States
28	Increasing DR Screening Through TOP: Supporting Implementation and Identifying Opportunities for Scale up in Ontario	Unknown status	No Results Available	•Diabetes Mellitus, Type 2 •Diabetes Mellitus, Type 1	•Other: a mail letter, a phone call and a phone call plus mailed letter	•Black Creek Community Health Centre, Toronto, Ontario, Canada •Women's College Hospital Family Health Team, Toronto, Ontario, Canada
29	Web-based Support During Pregnancy and Early Motherhood in Women With Type 1 Diabetes (MODIAB-web)	Completed	No Results Available	•Diabetes Type 1 •Pregnancy •Early Motherhood	•Other: web-based support	•Sahlgrenska Academy, Institute of Health Care Sciences, Gothenburg, Sweden
30	Incentives, Cognitive Training and Internet Therapy for Teens With Poorly Controlled Type 1 Diabetes	Completed	Has Results	•Type 1 Diabetes	•Behavioral: MAxIM •Behavioral: Usual Care	•Dartmouth College, Hanover, New Hampshire, United States
31	STEP: Social Support To Empower Parents	Completed	Has Results	•Type 1 Diabetes	•Behavioral: STEP	•University of Massachusetts, Worcester, Worcester, Massachusetts, United States
32	"POWER2DM Evaluation Campaign"	Unknown status	No Results Available	•Type1 Diabetes Mellitus •Type2 Diabetes Mellitus •Diabetes Mellitus •Health Behavior •Self Efficacy	•Device: POWER2DM system •Other: Usual care	•Leiden University Medical Centre, Leiden, Zuid-Holland, Netherlands •Reina Sofia University Hospital, Córdoba, Spain

	Title	Status	Study Results	Conditions	Interventions	Locations
33	Conception of a Diagnosis, Prognosis and Therapeutic Decision Tool for Patients With Autoimmunity and Inflammation	Not yet recruiting	No Results Available	•Autoimmune Lymphoproliferative Syndrome •Autoimmune Cytopenia •Autoimmune Diseases •Autoimmune Anemia •Autoimmune Thrombocytopenia •Autoimmune Hepatitis •Autoimmune Diabetes •Autoimmune Rheumatologic Disease •Systemic Lupus Erythematosus •Juvenile Idiopathic Arthritis •and 10 more	•Biological: Collection of samples	
34	Communication and Coping for Mothers of Adolescents With Type 1 Diabetes	Active, not recruiting	No Results Available	•Type 1 Diabetes Mellitus	•Behavioral: Communication & Coping Intervention •Behavioral: Education & Check Ins	•Vanderbilt University Medical Center, Nashville, Tennessee, United States
35	Parental Management of Young Children's Diabetes	Completed	No Results Available	•Type 1 Diabetes	•Behavioral: Parental Support •Behavioral: Diabetes Education	•Children's National Medical Center, Washington, District of Columbia, United States •Virginia Commonwealth University, Richmond, Virginia, United States
36	CoYoT1 to California	Active, not recruiting	No Results Available	•Type 1 Diabetes Mellitus	•Behavioral: CoYoT1 Care •Other: Standard Care	•Children's Hospital, Los Angeles, California, United States
37	Evaluation of a Mobile Application to Optimize Self-decision on Metabolic Control in Persons With Type 1 Diabetes	Completed	No Results Available	•Diabetes Mellitus, Type 1	•Other: PRE-test	•Universidad Iberoamericana, Santo Domingo, Distrito Nacional, Dominican Republic
38	Type 1 Diabetes- Collaboration Around Technology Using Community Health Workers	Recruiting	No Results Available	•Diabetes •Type 1 Diabetes •Young Adult •Diabete Mellitus	•Behavioral: T1D-CATCH	•Albert Einstein College of Medicine, Bronx, New York, United States
39	Feasibility Study of Family Teamwork Peer-Delivery	Completed	No Results Available	•Type 1 Diabetes	•Behavioral: Family Teamwork-Peer Delivery	•Texas Children's Hospital, Houston, Texas, United States
40	Peer i-Coaching for Activated Self-Management Optimization in Adolescents and Young Adults With Chronic Conditions	Recruiting	No Results Available	•Sickle Cell Disease •Chronic Kidney Diseases •Systemic Lupus Erythematosus •Childhood Cancer •Inflammatory Bowel Diseases •Stem Cell Transplant •Organ Transplant •Diabetes Mellitus, Type 1 •Cystic Fibrosis	•Behavioral: PiCASO Intervention Group •Behavioral: Sham Comparator: Attention Control Group	•Duke University, Durham, North Carolina, United States

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Unsworth R., Armiger R., Jugnee N., Thomas M., Herrero P., Georgiou P., Oliver N., Reddy M. Safety and Efficacy of an Adaptive Bolus Calculator for Type 1 Diabetes: a Randomised Controlled Crossover Study (Accepted for publication in the Diabetes Technology & Therapeutics journal 08.02.2023, not yet published)	**Figure 2.1:** ABC4D app interface for insulin dose advice **Figure 2.7:** ABC4D system overview **Figure 4.1:** Consort flow diagram **Figure 4.6:** Initial and Final ICRs in the intervention phase for Breakfast, Lunch and Dinner a) without exercise b) with Exercise **Table 4.1:** Baseline Demographic information for participants randomised and differences between the control first and intervention group first **Table 4.2**: Glycaemic outcomes for daytime (07:00-22:00) for the control and intervention periods **Table 4.3:** Glycaemic outcomes for night-time (22:00-07:00) for the control and intervention periods **Table 4.4:** Glycaemic outcomes for the 24-hour period for the control and intervention periods **Table 4.13:** Quality of life questionnaire and GOLD scores **Table 4.15:** App usage, insulin dose acceptance rate and magnitude of discrepancy between doses recommended and doses participants recorded as taken.	107 122 140 166 141 145 146 147 156 159	Mary Ann Libert, Inc. Publishers	Permission granted

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