Individualised Assessment and Management of Diabetes in Pregnancy

Dr Tara Lee
MBBS MA(Cantab) MRCP(UK) MRCOG

University of East Anglia, Norwich Medical School
2025

This dissertation is submitted for the degree of Doctor of Philosophy
Date of submission: April 2025

Abstract

Background

Type 1 diabetes in pregnancy is associated with an increased risk of complications for both mother and fetus. Maternal glycaemia is a major modifiable risk factor in reducing these risks, however, despite improvements in diabetes management, rates of complications remain high. Outside of pregnancy, hybrid closed-loop therapy is associated with improved glycaemia for adults and children with type 1 diabetes. Whilst hybrid closed-loop therapy shows promise for managing type 1 diabetes during and immediately after pregnancy, its clinical efficacy remains unclear. Furthermore, currently guidelines do not specifically address the postpartum period when further challenges including the demands of caring for a newborn are great.

Objectives

To evaluate the clinical efficacy and safety of hybrid closed-loop therapy compared to continuous glucose monitoring and standard insulin therapy during pregnancy and the first six months postpartum.

Methods

We performed a multicentre parallel-group controlled trial where pregnant women with type 1 diabetes were randomised to continue standard insulin therapy with continuous glucose monitoring or to hybrid closed-loop therapy. Assigned treatments were continued from randomisation in early pregnancy until six months' postpartum.

Findings

CamAPS FX hybrid closed-loop therapy improves maternal glycaemia during pregnancy and the first six months' postpartum (10.5% and 15% respectively). Women using hybrid closed-loop during pregnancy gained less weight and developed fewer hypertensive disorders. Women reported preference for hybrid closed-loop over standard insulin therapy during pregnancy and into the postpartum period. Trial healthcare professionals also supported hybrid closed-loop therapy as standard of care for the management of type 1 diabetes during pregnancy.

Conclusions

My research has demonstrated that hybrid closed-loop is an effective treatment option providing clinical advantage over and above continuous glucose monitoring with standard insulin therapy. These results informed the NICE technical appraisal recommendations that hybrid closed-loop therapy should be offered to all pregnant women with type 1 diabetes.

Table of Contents

List of figures and tables

For AHL

Acknowledgements

Firstly, I would like to thank my primary supervisor, Helen Murphy. Thank you for believing in me and making me believe that I could be a clinical researcher. Thank you for all your encouragement, guidance and hours investing in me over the last four years.

Thank you to Charlie Bircher for agreeing to be my PhD co-supervisor and clinical supervisor. Thank you for keeping me grounded and reminding me that I have always loved being a clinician and obstetrician.

I would also like to thank Ken Hodson, Lucy MacKillop and Alastair McKelvey for formally and informally mentoring me over the last eight years and through my PhD. You have all been influential in shaping my career pathway in maternal medicine so far.

Thank you to the other inspirational diabetes professors and consultants I have met along this journey, including but not limited to Eleanor Scott, Robbie Lindsay, Rebecca Reynolds, Anna Brackenridge, Kate Hunt and Sara White. Thank you for keeping me company at conferences, being there for me during my talks and presentations and helping me to develop as a clinician and academic, I could not have done this without all of you either. I hope that we will continue to work together to improve care for women with diabetes in pregnancy.

Sara Hartnell, you deserve a thank you all to yourself. Thank you for teaching me everything I know about CamAPS FX and all those out of hours rescues. I feel so lucky to have met and worked with you.

To the Diabetes in Pregnancy team in Norwich, thank you for supporting me and my research in antenatal clinic. I do not think I would have considered doing a PhD in diabetes in pregnancy if I had not been scooped up by Fran Harlow and made to feel so welcome and part of the team as an SHO and first year registrar all those years ago. Nina Willer, Lou Harrison, Lauren Blake, you have been the absolute best cheerleaders and have stuck by me at my best and worst. Your dedication and care for the women we look after is second to none and I hope I get to work with you or DSMs like you as a consultant.

Thank you to the Diabetes Research and Wellness Foundation for all your support and for funding my fellowship.

My deepest thanks go to all the women with diabetes who took part in our studies and who I have had the pleasure of caring for over the last few years. Thank you for your patience and being so generous with your time. It has been such a real privilege getting to know you all; thank you for sharing with me even a fraction of what it is like living with diabetes. Without you, none of this research would have been possible.

Family and friends (old and new) have supported me through this fellowship. Thank you for being there for me, providing fortified beverages, fun adventures away from work, humorous memes and a friendly ear.

Last, and by no means least, my husband Andrew, thank you for your unwavering support. Thank you for always being there for me and your belief in me especially the many times when I did not think I could do it myself. I dedicate this thesis to you.

Word count

42,582 words

(Word count includes footnotes, the abstract and the bibliography, but excludes the title page; copyright statement; acknowledgements; table of contents; list of illustrations; tables and figures and their legends; and appendices.)

Abbreviations

ADE	Adverse Device Event
AF	Artificial Feeding
AID	Automated Insulin Delivery
AiDAPT	Automated insulin Delivery Amongst Pregnant women with Type 1 diabetes trial
BF	Breastfeeding
BMI	Body Mass Index
CEMACH	Confidential Enquiry into Maternal and Child Health
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CIRCUIT	Closed-loop Insulin delivery by glucose Responsive Computer algorithms in type 1 diabetes pregnancies trial
CLC-P	Pregnancy-specific zone model predictive controller based closed-loop control
CLIMB	Closed-Loop Insulin in Mothers with Type 1 Diabetes and Baby feeding practices study
CLIP	Closed-Loop in Pregnancy study
CONCEPTT	Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial
CRISTAL	Closed-loop insulin delivery in pregnant women with type 1 diabetes
CSII	Continuous Subcutaneous Insulin Infusion
CV	Coefficient of Variation
DDS	Diabetes Distress Score
DIY	Do-It-Yourself
DKA	Diabetic Ketoacidosis
eGFR	Estimated Glomerular Filtration Rate
EME	Efficacy Mechanism and Evaluation Programme
EQ-5D	Euroqol Five Dimensions Health-Related Quality of Life Questionnaire
GMI	Glucose Management Indicator
GROW	Gestation-Related Optimal Weight
HCL	Hybrid Closed-Loop

HCP	Healthcare Professional
HFSQ II	Hypoglycaemia Fear Survey Questionnaire
IFS	Infant Feeding Survey
INSPIRE	INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations questionnaire
IQR	Interquartile Range
ISCO-08	International Standard Classification of Occupations 2008
JDRF	Juvenile Diabetes Research Foundation, renamed Breakthrough T1D in Jan 2025
kJ	Kilo-Joules
MDI	Multiple Daily Injections
MDT	Multidisciplinary Teams
MPC	Model Predictive Controller
NHS	National Health Service
NICE	UK National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health and Care Research
NPID	National Pregnancy in Diabetes audit
PICLS	Pregnancy Intervention with a Closed-Loop System study
PROTECT	PRegnancy Outcomes using continuous glucose monitoring TEChnology in pregnant women with Type 2 diabetes study
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SD	Standard Deviation
SH	Severe Hypoglycaemia
T1D	Type 1 Diabetes
TAR	Time Above Range
TBR	Time Below Range
TDD	Total Daily Dose
TIR	Time In Range
UK	United Kingdom
WHO	World Health Organisation

Publications and statement of authorship

The research reported is my own original work, which was carried out in collaboration with others as follows:

Chapter 1: Summary of the background literature – written by Tara Lee.
This chapter is an updated review where parts were previously published as the following review paper:

> **Lee TTM,** Murphy HR. What's new in the management of type 1 diabetes in pregnancy? Br J Hosp Med. 2022 Dec 2;83(12):1–10.

TTML researched and wrote this paper under HRM's supervision and expert input.

Chapter 2: Biomedical results of the main AiDAPT trial.
This chapter is an adaptation of the following published paper of which Tara Lee was the lead author:

> **Lee TTM,** Collett C, Bergford S, Hartnell S, Scott EM, Lindsay RS, et al. Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes. New England Journal of Medicine. 2023 Oct 26;389(17):1566–78.

Author contributions:
TTML co-designed the study (contributing to the development and inclusion of post-covid amendments, addition of fetal growth, inpatient glycaemia and postpartum studies), recruited and provided support for trial participants, supported the preparation of results for the primary results publication and co-wrote the manuscript.

HRM, CC, EMS, RSL, KFH, DRM, RMR, MH, LS, JS, CK, RH also co-designed the study. SB and CK wrote the statistical analysis plan, carried out data analysis, including statistical analyses, with support from LS, JS and RB. CC, EF and MEW supported data collection. SH provided participant and healthcare professional device training including troubleshooting and clinical care. KB supported analysis of the patient-reported outcomes. DR, JL undertook and supported analysis of qualitative interviews. HRM, CC and SB co-wrote the manuscript. All authors reviewed and edited the manuscript.

Chapter 3: Psychosocial results of the AiDAPT trial - written by Tara Lee

This chapter summarises the findings of the qualitative studies associated with the AiDAPT pregnancy study. These data have been published as three qualitative papers:

- Lawton J, Kimbell B, Closs M, Hartnell S, **Lee TTM**, Dover AR, et al. Listening to Women: Experiences of Using Closed-Loop in Type 1 Diabetes Pregnancy. Diabetes Technology & Therapeutics. 2023 Dec;25(12):845–55.
- Lawton J, Rankin D, Hartnell S, **Lee TTM**, Dover AR, Reynolds RM, et al. Healthcare professionals' views about how pregnant women can benefit from using a closed-loop system: Qualitative study. Diabetic Medicine. 2023;40(5):e15072.
- Rankin D, Hart RI, Kimbell B, Barnard-Kelly K, … **Lee TTM,** … et al. Rollout of Closed-Loop Technology to Pregnant Women with Type 1 Diabetes: Healthcare Professionals' Views About Potential Challenges and Solutions. Diabetes Technology & Therapeutics. 2023 Apr 1;25(4):260–9.

Author contributions:

TTML was involved in reviewing and discussing preliminary findings in order to develop a framework for the results presentation and to support clinical obstetric recommendations and contributed to the recommendations for rollout of closed-loop therapy from this study. TTML reviewed, edited and approved the final versions of these papers.

Specialist qualitative input including study design, data collection and analysis and manuscript writing from JL, DR, RIH and BK.

Chapter 4: Postpartum use of hybrid closed-loop therapy, an AiDAPT extension study

This chapter is an adaptation of the following published paper of which Tara Lee was the lead author:

> **Lee TTM,** Collett C, Bergford S, Hartnell S, Scott EM, Lindsay RS, et al. Automated insulin delivery during the first 6 months postpartum (AiDAPT): a prespecified extension study. The Lancet Diabetes & Endocrinology. 2025 Mar 1;13(3):210–20.

Author contributions:

TTML co-designed this extension study, recruited and provided support for trial participants and co-wrote the manuscript.

The statistical analysis plan was written with input from CK, SB, and JS. SB and HRM co-wrote the manuscript. All authors reviewed and edited the manuscript.

Chapter 5: Discussion - written by Tara Lee

Chapter 1: Introduction and Background

1.1 Overview

In the UK, out of approximately 700,000 pregnancies a year, around 35,000 (5%) are affected by diabetes. The majority of those 35,000 pregnancies are complicated by gestational diabetes (85%) with the remainder complicated by pre-gestational diabetes, of which 6% is affected by type 1 diabetes (1–5). National population data demonstrates increasing prevalence of type 1 diabetes in pregnancy over the past two decades (6).

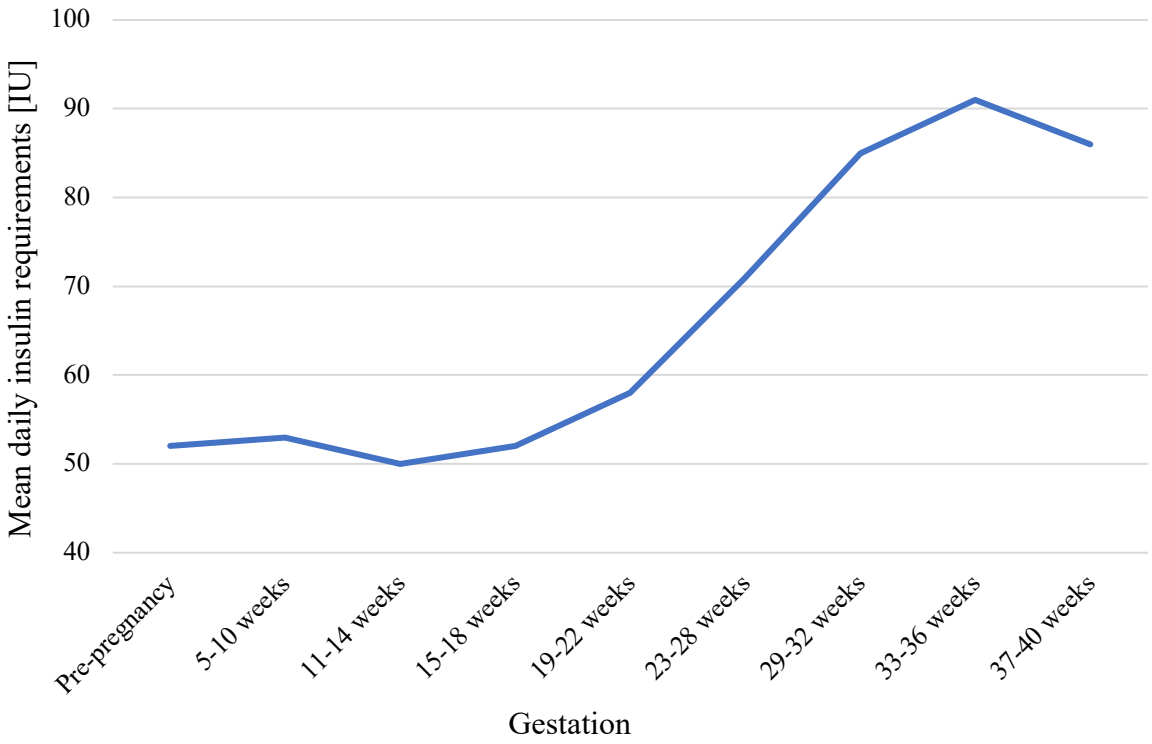
During pregnancy, type 1 diabetes is associated with an increased risk of complications to both mother* and fetus. Risks to the mother include both diabetes and pregnancy-related complications with increased severe hypoglycaemia and diabetic ketoacidosis events and the potential for worsening of pre-existing diabetic retinopathy, nephropathy and neuropathy alongside a doubling in the rates of major congenital anomalies, and a three to five-fold increased rate of stillbirth and neonatal death. One in two pregnancies are complicated by preterm births, large for gestational age babies, and admission to neonatal care units with problems such as respiratory distress, hyperbilirubinaemia and hypoglycaemia (6,8–10).

It is well established that optimal glycaemia prior to and during pregnancy can reduce the risk of obstetric and neonatal complications (11,12). However, managing to achieve and maintain optimal day-to-day glucose levels throughout pregnancy is challenging owing to a combination of multiple gestational changes (Figure 1.1). Initially during the first trimester, initial physiological changes in insulin sensitivity, increased efforts to achieve tighter pregnancy targets and possible nausea and vomiting of pregnancy compound to increase rates of severe hypoglycaemia events with potentially severe consequences for the mother (13–15).

* This thesis uses the terms “woman” or “mother” to minimise misrepresentation of health statistics and cross-cultural communication barriers, and maintain visibility of the unique needs, experiences, and rights that come with pregnancy, birthing, and breastfeeding. These terms should be taken to include people who do not identify as women but are pregnant or have given birth, recognising that inclusivity and consideration of additional medical and social needs for this group require unique attention (7).

Following this, from the time of placental development in the second trimester into the third trimester, increasing peripheral insulin resistance as well as leads to increasing insulin requirements and frequent insulin dose adjustments (15–18). The underlying mechanism for an initial increase in insulin sensitivity in the first trimester is less well understood but thought to be related to decreasing levels of progesterone and human chorionic gonadotropin hormones as ongoing pregnancy support transitions from the corpus luteum to the placenta (19–21). The increasing insulin resistance observed later in pregnancy has traditionally been attributed to placental hormones: human placental lactogen and progesterone (22,23). More recently, placentally synthetised tumour necrosis factor-α has been shown to correlate with insulin resistance however studies examining correlations between placental hormones and insulin resistance have been in the gestational diabetes rather than the type 1 diabetes pregnant population (24–26).

Figure 1.1 Changes in insulin requirements throughout pregnancy in type 1 diabetes (adapted from Skajaa et al 2018) (15)



In addition to these changing insulin requirements due to gestational changes in insulin sensitivity and resistance, there is an increased day-to-day variability in insulin resistance and increasing time to peak insulin concentration which further complicate daily insulin dosing (27–29). All these factors and challenges exacerbate diabetes distress and the increase the

enormous daily burden of self-care. Pregnancy can be a worrying and anxious time for many women, and the added physiological, pharmacological and psychological challenges of managing type 1 diabetes should not be underestimated (30,31).

Despite many advances in the care of women with type 1 diabetes in pregnancy, suboptimal maternal glycaemia persists as does high rates of large for gestational age babies (>50%), preterm births (40%) and neonatal intensive care unit admissions (40%) (6). A contemporary nationwide cohort study found that only 16% of women with type 1 diabetes achieved target glycaemia in early pregnancy, as defined in the 2015 UK NICE (National Institute for Health and Care Excellence) clinical guidelines: haemoglobin A1c (HbA1c) of <48mmol/mol, with 42% achieving it by late pregnancy (6).

We have not yet established how to support the majority of pregnant women with type 1 diabetes to achieve target glucose levels and optimal pregnancy outcomes. This is reflected in the James Lind Alliance Diabetes and Pregnancy Priority Setting Partnership's top ten research priorities. These questions were identified through a series of stages working with 750-1000 women, their support networks (friends and family) and healthcare professionals as per established James Lind Alliance methodology (32). The final list of ten James Lind Alliance questions were chosen and ranked as demonstrated in Figure 1.2 (33).

Figure 1.2 Diabetes and pregnancy priority setting partnership's top ten infographic (www.jla.nihr.ac.uk/priority-setting-partnerships/diabetes-and-pregnancy/) (33)

This thesis will add to the current evidence base to improve the care of women with type 1 diabetes and their babies. Specifically, I aim to address the following top priority research questions:

1: "How can diabetes technology be used to improve pregnancy, birth and mother and child health outcomes?" (Diabetes Pregnancy research priority 1)

2: "What are the specific postnatal care and support needs of women with diabetes and their infants?" (Diabetes Pregnancy research priority 6)

1.2 Management of type 1 diabetes in pregnancy

1.2.1 Glucose monitoring, maternal glycaemia and pregnancy glucose targets

Current NICE guidelines recommend the measurement of HbA1c at the beginning of pregnancy to "determine the level of risk to that pregnancy" in women with pregestational diabetes (type 1 and type 2 diabetes). They cite a level of 48mmol/mol, above which the risk of complications increases. They also recommend that measurement of HbA1c during the second and third trimester is to be considered but not used routinely "to assess a woman's blood glucose control" (34). This is due to the physiological effects of pregnancy on HbA1c, which impact the interpretation of laboratory HbA1c measures in each trimester. Outside of pregnancy, HbA1c has been shown to be a useful measure of average glycaemia over the preceding two to three months and is a helpful marker for determining risk of diabetes complications. However, in early pregnancy HbA1c levels are often lower due to higher turnover of erythrocytes and a drop in fasting glucose levels between six and 14 weeks' gestation (35–39). During later pregnancy, the so-called glycation gap, potentially contributes to higher HbA1c levels, compared to mid-gestation (40). Despite these well recognised limitations and in the absence of better alternatives, HbA1c has been used as a marker of overall maternal glycaemia and to assess change throughout pregnancy by serial measurements.

In addition to HbA1c, during pregnancy, women with type 1 diabetes traditionally monitor their blood glucose levels by serially sampling capillary blood glucose by finger-prick at least 7 times a day: fasting, before and one hour after each meal, and before bed. Women are recommended to aim for a fasting glucose of <5.3mmol/L and 1-hour postprandial glucose levels of <7.8mmol/L if "achievable without problematic hypoglycaemia" (34). Finger-prick

testing however, only gives snapshots of glycaemia at the time of testing with limited reflection of glucose exclusions in between these tests.

Over the past two decades newer technologies for continuously monitoring interstitial glucose levels have become available which are now grouped together as continuous glucose monitoring systems (CGM). Whilst early CGM systems were burdensome, with frequent errors, more recent devices have become smaller, more user friendly, with accuracy comparable to capillary glucose monitoring and are now approved for widespread clinical use. The most recent systems are accurate for insulin dosing and can replace traditional capillary blood glucose monitoring by finger-prick (41).

1.2.2 Continuous glucose monitoring

CGM systems are made up of 3 components:

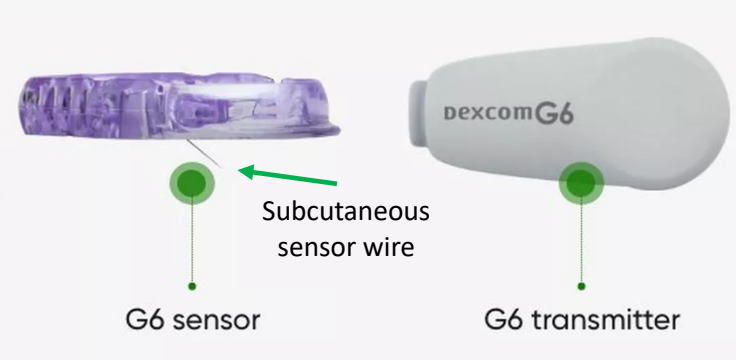
- a sensor which measures interstitial glucose
- a transmitter which stores and sends glucose data using Bluetooth to a display device
- a display device (which can be a device-specific receiver, the user's smartphone or smart watch via an application).

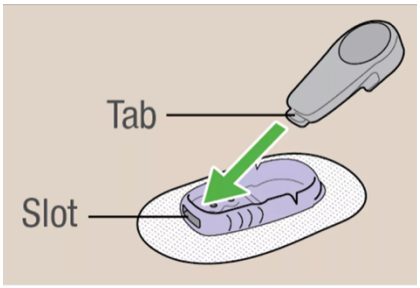
Current real-time CGM sensors can measure glucose levels every one to five minutes (around 300 measurements a day) and send these readings automatically to the display device. This is in contrast to the flash- or intermittently-scanned continuous glucose monitors, with which users are required to physically bring the reader close to the sensor in order to view stored glucose levels. With both, alarms and alerts can be set up to notify the user of any deviations in glucose level outside a set range (high or low) and with real-time predicted rate of change. With real-time CGM, these levels can also be shared with 'followers' (partners, parents etc) in real time.

There are many CGM systems manufactured by different companies (Table 1.1). They vary in terms of the site and lifespan of the sensor and transmitter; how data is transferred by Bluetooth; duration of device warm-up time prior to measuring glucose and user requirements for optimal use. In some systems, the sensor and transmitter are integrated into a single physical device. The most common real-time CGM systems used in the UK are the Abbott Freestyle Libre systems (Illinois, United States), Dexcom systems (California, United States) and the Medtronic Guardian systems (Minnesota, United States). Systems from these

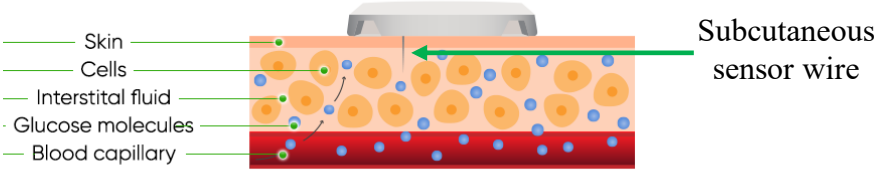
manufacturers have external sensors and transmitters which sit on the skin with a subcutaneous sensing wire. In contrast, the Eversense CGM systems comprise of a small implantable sensor that is placed 3-5mm below the skin by a trained Eversense provider who inserts the sensor subcutaneously under local anaesthetic via a 5mm incision. The sensor stays in place, if no complications, for up to a year depending on the system. During use, a transmitter is secured over the skin where the sensor is situated using an adhesive patch. The transmitter is reusable up to a year but requires daily charging. Further sensors require removal and replacement by minor procedures under local anaesthetic performed by trained Eversense providers.

Figure 1.3 Examples of different CGM sensors and transmitters
A. Example of external sensor and separate external transmitter: Dexcom G6 CGM





B. Example of external integrated sensor and transmitter: Dexcom G7 CGM



C. Example of implantable sensor with separate external transmitter: Eversense CGM

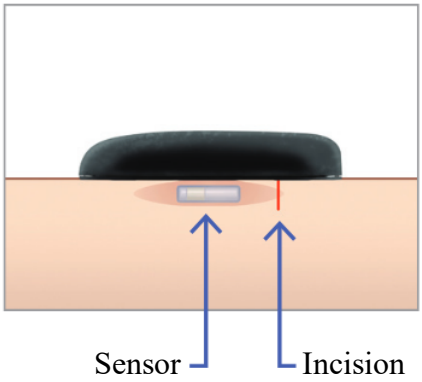


Table 1.1 Summary and comparison of widely used CGM systems (2024)

CGM system	Sensor	Transmitter	Site of application	Compatible receiving & display device	Warm up times & calibration
Dexcom One+	10 day self-applied external disposable sensor with integrated transmitter. Measures levels every 5 minutes.		Back of upper arm, abdomen	Smartphone app Dexcom One+ receiver Apple Watch	• 30 minutes, no calibration
Dexcom G6	10 day self-applied external disposable sensor measures levels every 5 minutes.	3-month external disposable transmitter.	Back of upper arm, abdomen	Smartphone app Dexcom G6 receiver	• 2 hours, no calibration
Dexcom G7	10 day self-applied external disposable sensor with integrated transmitter. Measures levels every 5 minutes.		Back of upper arm	Smartphone app Dexcom G7 receiver Apple Watch	• 30 minutes, no calibration
Abbott Freestyle Libre2	14 day self-applied external disposable sensor with integrated transmitter. Measures levels every minute.		Back of upper arm	Smartphone app Freestyle Libre2 receiver	• 1 hour, no calibration
Abbott Freestyle Libre3	14 day self-applied external disposable sensor with integrated transmitter. Measures levels every minute.		Back of upper arm	Smartphone app Freestyle Libre3 receiver	• 1 hour, no calibration
Medtronic Guardian 4	7 day self-applied external disposable sensor measures levels every 5 minutes.	Rechargeable separate transmitter. 7 day lifespan if fully charged. Lasts up to 1 year.	Back of upper arm	Smartphone app	• 2 hour warm up time • Requires regular calibration with capillary blood glucose levels (every 12 hours after first 2 and 6 hours post insertion)
Medtronic Simplera	7 day self-applied external disposable sensor with integrated transmitter. Measures levels every 5 minutes.		Back of upper arm	Smartphone app	• 2 hours, no calibration
Eversense E3	6 month implantable sensor. Needs placement and removal by trained Eversense inserter.	Rechargeable separate transmitter. Sits on the skin over the site of sensor with adhesive patch. Requires daily charging.	Upper arm	Smartphone app	• 24 hour warm up time • Requires calibration with capillary blood glucose levels (4 tests in the first 36 hours after warm-up; up to 2 calibrations a day for the first 21 days, then either once / twice a day).
Eversense 365	1 year implantable sensor. Needs placement and removal by trained Eversense inserter.	Rechargeable separate transmitter. Sits on the skin over the site of sensor with adhesive patch. Requires daily charging.	Upper arm	Smartphone app	• 24 hour warm up time • Requires calibration with capillary blood glucose levels (4 tests in the first 36 hours after warm-up; daily for the first 13 days, then once a week).

The first major randomised controlled trial to examine the effectiveness of CGM was performed in 2008 (42). In this study 322 adults and children with a baseline HbA1c between 53.0 – 86mmol/mol (7.0 – 10.0%) were randomly assigned either CGM or finger-prick capillary blood glucose monitoring and were followed up for 26 weeks. Patients were grouped into three age groups: 8-14 years old, 15-24 years old and ≥ 25 years old. There was a significant improvement in HbA1c without increased hypoglycaemia in those ≥ 25 years old but not in the younger age groups. Interestingly, authors examined use of CGM during this 26 week period in each group and those in the oldest group used CGM the most, with use in the younger groups declining over time. 83% of those in the oldest group used CGM for at least 6 days per week compared to 30% and 50% in the 15-24 and 8-14 age groups respectively. Secondary analysis did demonstrate that in both the younger age groups, when CGM was used at least 6 days a week, the improvement in glycaemia was similar to that seen in the ≥ 25 years old group.

A further study by the same group assessed CGM vs. capillary blood glucose monitoring over 26 weeks in 129 adults and children with a mean baseline HbA1c 53mmol/mol (< 7.0%), reflecting those who were achieving the NICE recommended glucose targets (43). Here, authors also demonstrated an improvement in HbA1c and decrease in time spent <3.9mmol/mol in those using CGM compared to finger-prick capillary glucose monitoring. These findings have been replicated by further studies with similar results among those using insulin pumps and multiple daily injections, suggesting that the benefits of CGM use are widely applicable, regardless of insulin delivery method (44–49).

There are several aspects to CGM which facilitate the improvement in glycaemia. CGM provides a wealth of data and greater insight into glycaemic excursions and daily patterns of glycaemia. From these, many more metrics can be calculated by CGM reporting software that provides more information to users with diabetes and healthcare professionals which can guide insulin dosing and lifestyle choices. In a recent study of 40 individuals with diabetes using CGM, 87% indicated that food choices changed from using CGM, 48% indicated that CGM led to modification of their exercise pattern, and 90% indicated that CGM use contributed to a healthier lifestyle (50).

In 2017, the Advanced Technologies & Treatments for Diabetes consensus on use of continuous glucose monitoring identified the most useful CGM metrics for use in clinical practice (51).

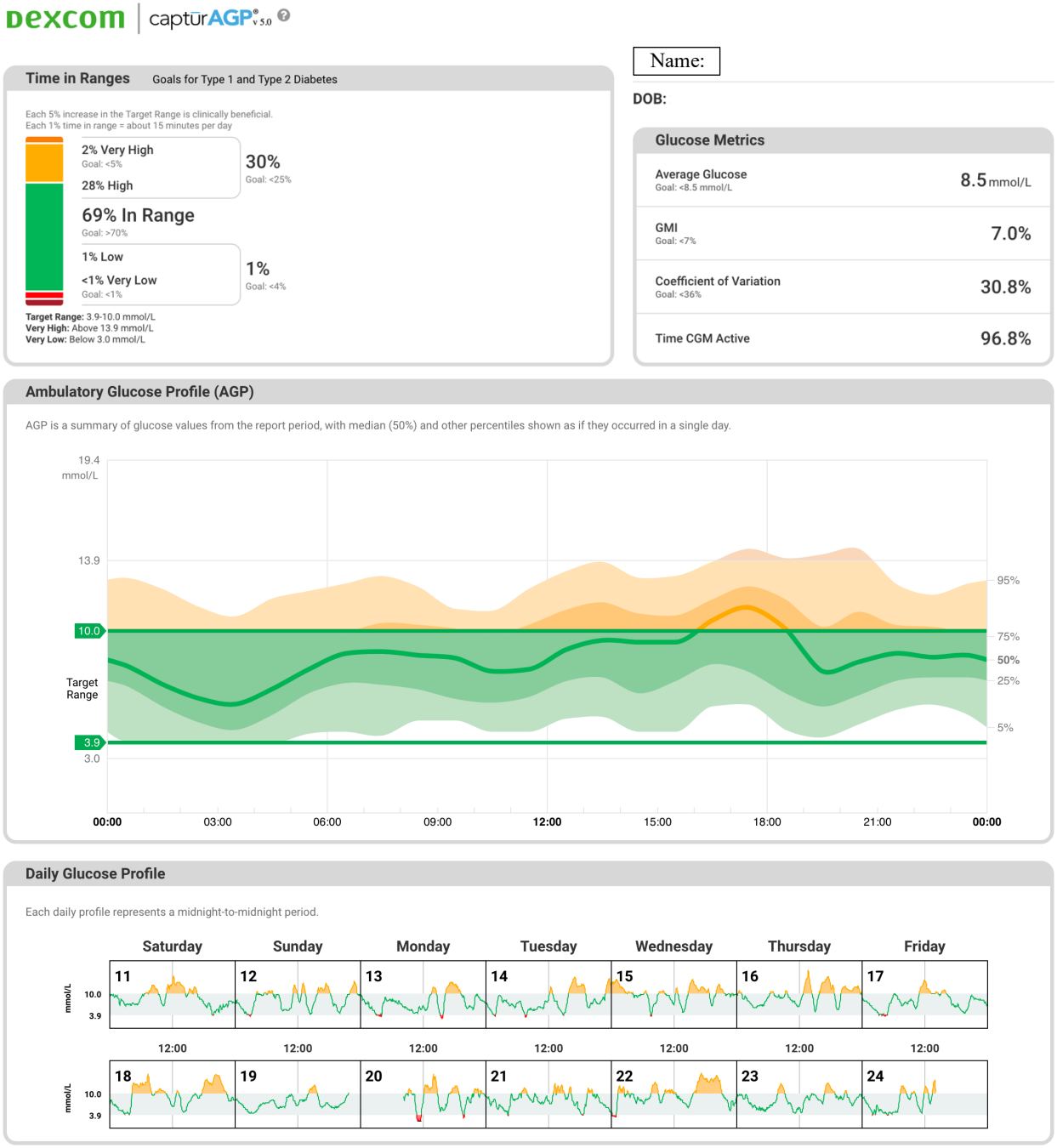
This was further streamlined by the 2019 Advanced Technologies & Treatments for Diabetes consensus group (Table 1.2) (52).

Table 1.2 Standardised CGM metrics for clinical care
(adapted from Advanced Technologies & Treatments for Diabetes International Consensus on Time in Range group 2019) (51)

1. Number of days CGM worn (recommend 14 days)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator (GMI)	
5. Glycaemic variability (%CV, coefficient of variation) target ≤ 36%	
6. Time above range (TAR): % of readings and time >13.9mmol/L	Level 2 hyperglycaemia
7. Time above range (TAR): % of readings and time 10.1 - 13.9mmol/L	Level 1 hyperglycaemia
8. Time in range (TIR): % of readings and time 3.9 - 10.0mmol/L	
9. Time below range (TBR): % of readings and time 3.0 - 3.8mmol/L	Level 1 hypoglycaemia
10. Time below range (TBR): % of readings and time < 3.0mmol/L	Level 2 hypoglycaemia
Use of ambulatory glucose profile for CGM report	

These metrics are recommended to be used in conjunction with lab-measured serum HbA1c and meaningful interpretation is dependent on sufficient glucose data upon which they are calculated. Metrics calculated from at least 70% CGM use in 14 days has been shown to correlate with and reflect glycaemia over the previous 3 months (53,54). Included in these metrics is the glucose management indicator, the term used for estimating HbA1c from the mean glucose as measured by CGM (55). CGM reporting software also generates ambulatory glucose profiles which offer users and healthcare professionals a pictorial view of glycaemic patterns on a daily or average basis (Figure 1.4). This can be especially informative for identifying glucose patterns for example identifying where in the 24hr day the above target glucose levels occur more commonly such as after the evening meal in the below illustration.

Figure 1.4 An example of ambulatory glucose profile



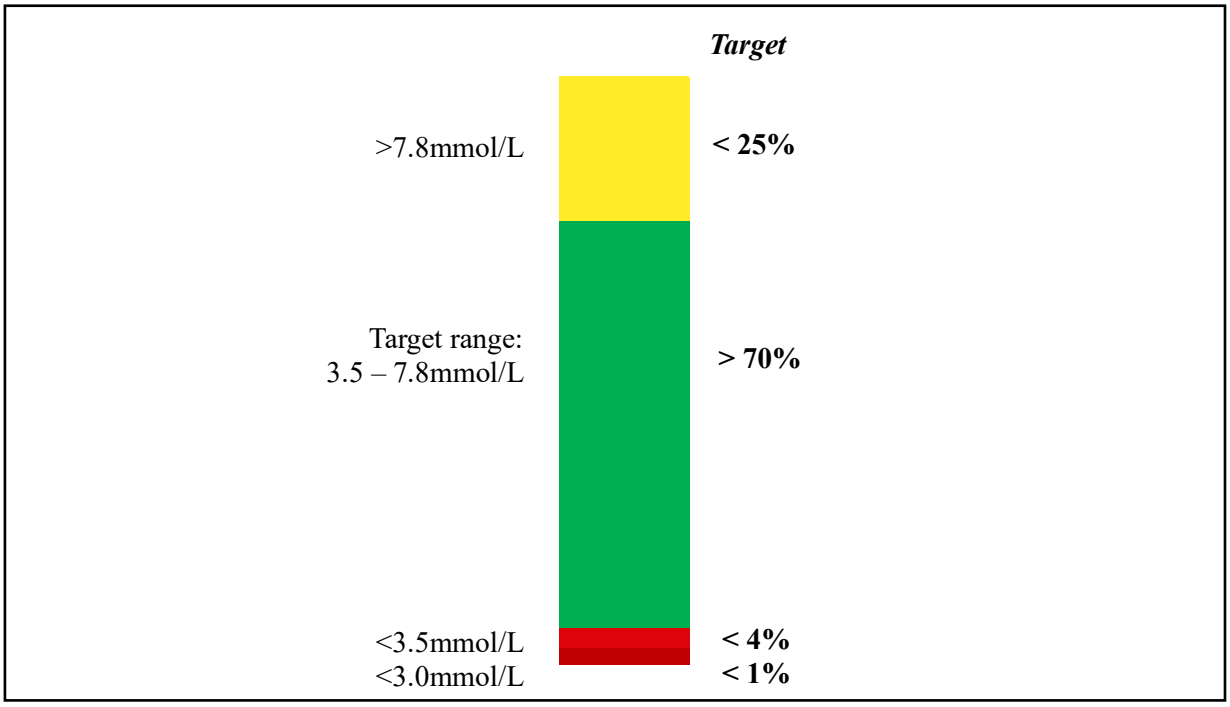
1.2.3 Continuous glucose monitoring in pregnancy

In pregnancy, the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) is a multicentre randomised controlled trial, comparing home glucose monitoring using finger-stick capillary blood glucose monitoring with CGM (56). This is the largest trial evaluating the use of CGM before and during pregnancy. It is also the first trial where CGM use was continuous from randomisation until delivery rather than intermittent. 325 women were recruited from 31 centres across six countries, 215 pregnant and 110 participants who were planning pregnancy (57). The results demonstrated that women using CGM in pregnancy had improved glycaemia at 34 weeks' gestation, as measured by an increased percentage of time in the pregnancy-specific target glucose range (between 3.5 - 7.8mmol/L: 68 vs. 61%) with less time spent hyperglycaemic (>7.8mmol/L: 27 vs. 32%) and no increase in severe hypoglycaemia (18 vs. 21 episodes), diabetes ketoacidosis (two episodes each) and duration or frequency of hypoglycaemia. The CGM treatment benefits were comparable for women using multiple daily injections or insulin pumps. This study also found that women using CGM during pregnancy delivered fewer large for gestational age babies (OR 0.51, 95% CI 0.28–0.90), who required fewer and shorter neonatal intensive care unit (NICU) admissions >24 hours (OR 0.48, 95% CI 0.26–0.86) and experienced fewer events of neonatal hypoglycaemia requiring treatment with IV dextrose (OR 0.45, 95% CI 0.22–0.89). By yielding a number needed to treat of six to prevent one NICU admission or one large for gestational age baby and eight to prevent neonatal hypoglycaemia, these data led to an update of the NICE Diabetes in Pregnancy guidelines in 2020, to recommend real-time CGM use in pregnancy for women with type 1 diabetes (34).

Similar to outside of pregnancy, there are several CGM metrics which are useful in antenatal clinical care. These include the time in range, time above range, time below range, measures of glucose variability: percentage coefficient variant and standard deviation, and measures of overall glycaemia: average glucose and glucose management indicator. In 2019, the Advanced Technologies & Treatments for Diabetes International Consensus on Time in Range put together recommendations for target glucose levels. In pregnancy these are >70% time spent in the pregnancy-specific target range (3.5 - 7.8mmol/L) with < 25% time spent above range and < 5% time spent below range from as early as possible in pregnancy (52). An important distinction between pregnant and non-pregnant individuals is that to minimise the risk of obstetric and neonatal complications the glucose targets are substantially more stringent during pregnancy,

with a much narrower target range of 3.5 - 7.8mmol/L compared to 3.9 - 10.0mmol/L outside of pregnancy (Figure 1.5).

Figure 1.5 CGM targets for type 1 diabetes in pregnancy
(adapted from Battelino et al 2019) (52)



These CGM metrics have been examined in pregnancy for their utility in relation to HbA1c and prediction of obstetric and neonatal complications.

Access to CGM reporting software and CGM metrics has added another dimension to diabetes self-care in pregnancy. The value of CGM in food selection and informing the timing of pre-meal insulin boluses is particularly important for achieving the tight post-meal pregnancy glucose targets. Furthermore, the real-time nature of real time-CGM and ability to set customisable alerts and safety alarms also helps facilitate women to work towards if not achieve the tight pregnancy glucose targets and together reduce obstetric and neonatal adverse outcomes.

A study by Law et al. examined the relationship between average glucose levels as measured by CGM and HbA1c by using serial measures of both in pregnancy (58–60). They demonstrated a linear relationship between average CGM glucose levels and HbA1c during pregnancy. However, compared to the non-pregnant population, the gradient of this relationship is shallower, meaning that for each 11.1mmol/mol reduction of HbA1c in pregnancy, there is a

smaller decrease in average glucose (0.67mmol/L vs. 1-2mmol/L) compared to outside of pregnancy (60,61). They suggested that an average target glucose of 6.4 - 6.7mmol/L would be equivalent to achieving a HbA1c of 42mmol/mol in pregnancy. Clinically this means that the glucose management indicator and mean CGM glucose can be used as an adjunct to laboratory measures of HbA1c for assessing glycaemia in pregnancy.

Further studies have also examined the relationship between these CGM metrics and obstetric and neonatal outcomes. Kristensen et al performed an observational study of 186 pregnancies in women with type 1 diabetes using either real time-CGM or intermittently scanned CGM (62). Raised average glucose levels in the second and third trimester were associated with large for gestational age babies and increased time spent in the pregnancy-specific target range (by 5-7%) in the same trimesters were associated with lower rates of large for gestational age birthweight. Secondary analysis from CONCEPTT analysed CGM metrics from three time-points in pregnancy: 10-12 weeks, 24-25 weeks and 34-35 weeks' gestation and examined for relationships between these metrics and large for gestational age birthweight and other obstetric and neonatal complications (63). Overall a 5-7% higher time in range was associated with a reduction in large for gestational age birthweight, neonatal hypoglycaemia and neonatal intensive care unit admissions.

Several studies suggest that the majority of women do not meet the International Consensus on Time in Range CGM sensor glucose recommended pregnancy glucose targets. In CONCEPTT, 10% of women achieved >70% time spent in pregnancy-specific target range in the first and second trimesters with 34% managing to by the third trimester (57). Importantly, data from these studies also show that every 5% of time spent in range improvement confers additional benefit to the developing fetus (64).

1.2.4 Insulin therapy in pregnancy

Women with type 1 diabetes administer insulin to manage their glucose levels in different ways. Traditionally, most pregnant women used multiple daily injections, usually in regimens consisting of at least 3-4 short-acting insulin boluses and 1-2 injections of long-acting basal insulin each day. They may also give additional correction doses if their glucose levels are high. Increasingly, women are using insulin pumps before and during pregnancy. The rate of insulin pump use has increased with approximately 22% of UK women now entering pregnancy

using insulin pump therapy, and others swapping from multiple daily injections to insulin pump therapy in early pregnancy.

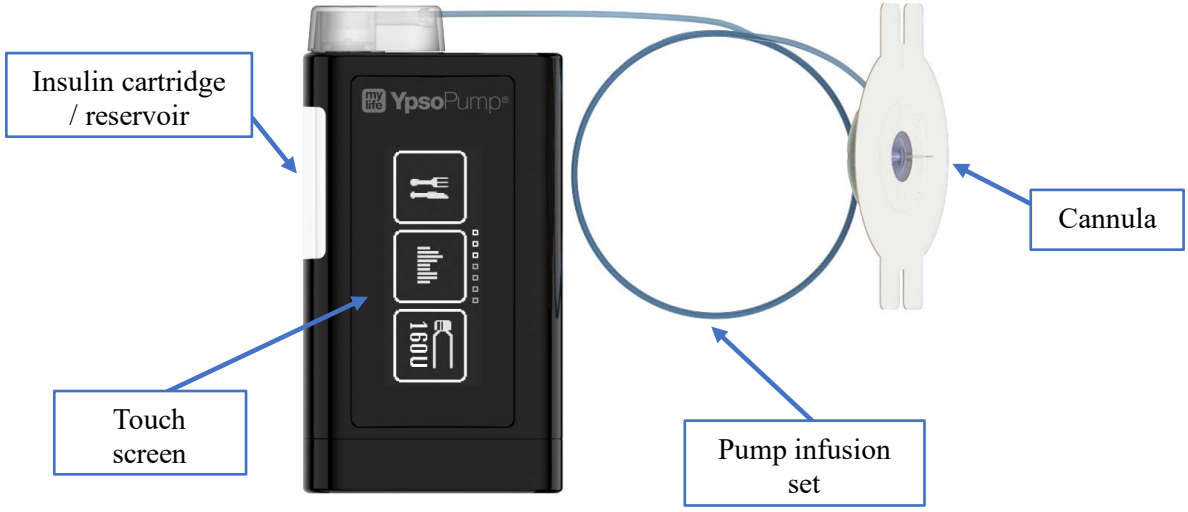
Insulin pumps have been available for over 40 years. In contrast with multiple daily injections, they continuously infuse small volumes of short-acting insulin into the subcutaneous space and thus are sometimes called continuous subcutaneous insulin infusion (CSII). Whilst there are ever increasing models and brands of insulin pumps, they can be categorised into two broad categories: tethered pumps and patch pumps. Tethered pumps comprise of an insulin pump, usually with control buttons and a screen built in, which then administers insulin from a refillable insulin reservoir or pre-filled cartridge via an infusion set (a tube that connects the pump to the pump cannula that sits subcutaneously). Patch pumps tend to comprise of a reservoir of insulin that sits directly on the skin and a short cannula that goes from the underside of the reservoir directly through the skin to the subcutaneous space. Patch pumps are then controlled using a smartphone application or "personal diabetes manager" handset that communicates via Bluetooth. When the reservoir is empty, it is disposed of and a new reservoir is placed and paired with the smartphone or handset.

The rate of insulin infusion can be adjusted hour by hour as a basal rate and users can give themselves pre-meal and correction boluses via the same pump. Many insulin pumps have bolus calculators integrated into their software (either on the pump itself or as part of a linked smartphone application) that facilitates more accurate pre-meal bolus dosing calculations. These bolus calculators have a user interface which allows users to input the number of grams of carbohydrates they are about to consume, and a dose is calculated based on their pre-programmed insulin to carbohydrate ratios. Many insulin pumps have software that also keeps track of how much basal and bolus insulin has been administered in order to calculate "insulin on board" or "active insulin" time. This information can be used to further adjust insulin dose calculations and minimise the risk of hypoglycaemia.

Insulin pump users are encouraged to change their infusion or cannula sets (tethered pumps) or pod / patch (patch pumps) at least every three days, if not more regularly in order to maintain good insulin absorption.

Figure 1.6 Examples of tethered vs. patch pumps

A. Example of tethered pump: Ypsomed YpsoPump



B. Example of patch pump: Omnipod

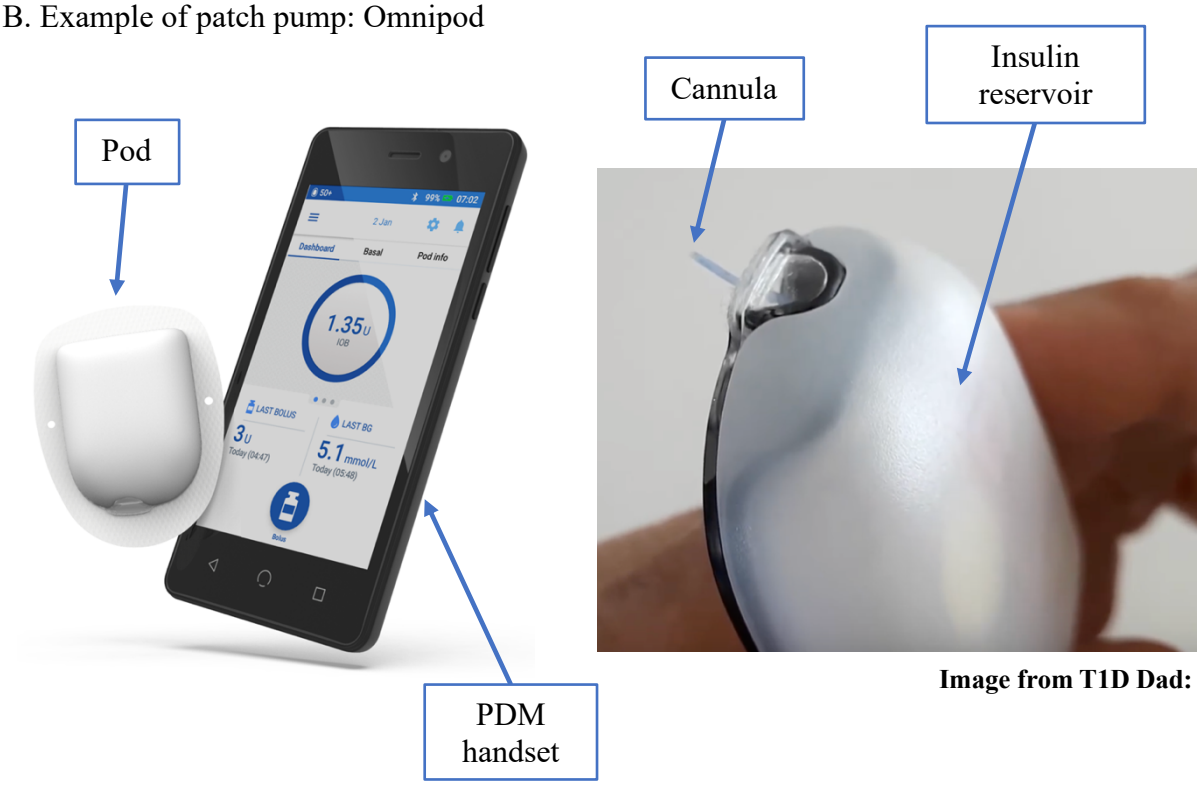


Image from T1D Dad:

Outside of pregnancy, insulin pump users have been shown to have better glycaemia, fewer severe hypoglycaemic events and improved quality of life (65). In the context of the stringent pregnancy glucose targets, this hourly customisation of the overnight basal rates compared to a single long-acting injection of insulin could help women achieve >70% time in the pregnancy-specific target range. Furthermore the flexibility of administering insulin boluses before meals and snacks exceeding 10-15 grams of carbohydrate, without needing to give additional painful and/or inconvenient subcutaneous injections, may also facilitate improved post-prandial glucose levels.

1.2.5 Use of insulin pump therapy in pregnancy

Despite the theoretical benefits in pregnancy, and good evidence regarding the benefits of using insulin pump therapy outside of pregnancy, the literature fails to demonstrate a benefit of insulin pumps over multiple daily injections during pregnancy. A systematic review, published in 2015, identified seven observational studies comparing insulin pumps and multiple daily injections in pregnant women with type 1 diabetes (66). From these, the authors concluded that there was no difference in maternal glycaemia as measured by HbA1c between the two modalities of insulin administration. However, the strength of this conclusion was low given the observational nature of the studies and the heterogenicity of study populations, follow up and outcomes. Sample sizes were small and the data were insufficient to draw conclusions about obstetric and neonatal outcomes. These findings were replicated in a Cochrane review which included five randomised controlled trials (67). However, the majority of these trials were conducted 25-30 years ago, using older generation pumps and pre-dated CGM use.

A recent pre-specified analysis of the CONCEPTT study, assessed between group (insulin pump versus multiple daily injections) change in HbA1c from randomisation to 34 weeks' gestation (68). 248 women were recruited with randomisation stratified for baseline insulin delivery modality (insulin pump vs. multiple daily injections) and baseline HbA1c. This ensured that the starting glycaemia of women using insulin pumps and injections were similar during early pregnancy (approximately 11-12 weeks' gestation). Unexpectedly, the authors found that by 34 weeks' gestation, women using multiple daily injections had greater improvements in HbA1c. The CGM glucose metrics were consistent with this, demonstrating that women using multiple daily injections also spent 5% more time in the pregnancy-specific target range (53% vs. 48%) during mid-pregnancy, consistent with the subsequent changes in HbA1c. In terms of obstetric and neonatal outcomes, insulin pump users experienced more hypertensive conditions (mostly

gestational hypertension: 14.4 vs. 5.2%), more neonatal hypoglycaemia (31.8 vs. 19.1%) and more neonatal intensive care admissions (44.5 vs. 29.6%). Both groups had the same rate of maternal hypoglycaemia events, however, insulin pump users did report less hypoglycaemia fear.

The difference in time spent in target range between insulin pump users and multiple daily injection users at 24 weeks' gestation was examined more closely by applying functional data analysis alongside the standard CGM metrics of CONCEPTT data (69). At 24 weeks, women using insulin pumps had higher glucose levels during the 24-hr day most notably between 0300 - 0600, 1300-1800 and 2030-0030. These patterns suggest prolonged postprandial hyperglycaemia after lunch and dinner, which is harder to manage with advancing gestation, because of increasing peripheral insulin resistance and a longer time to peak insulin concentration (28,29).

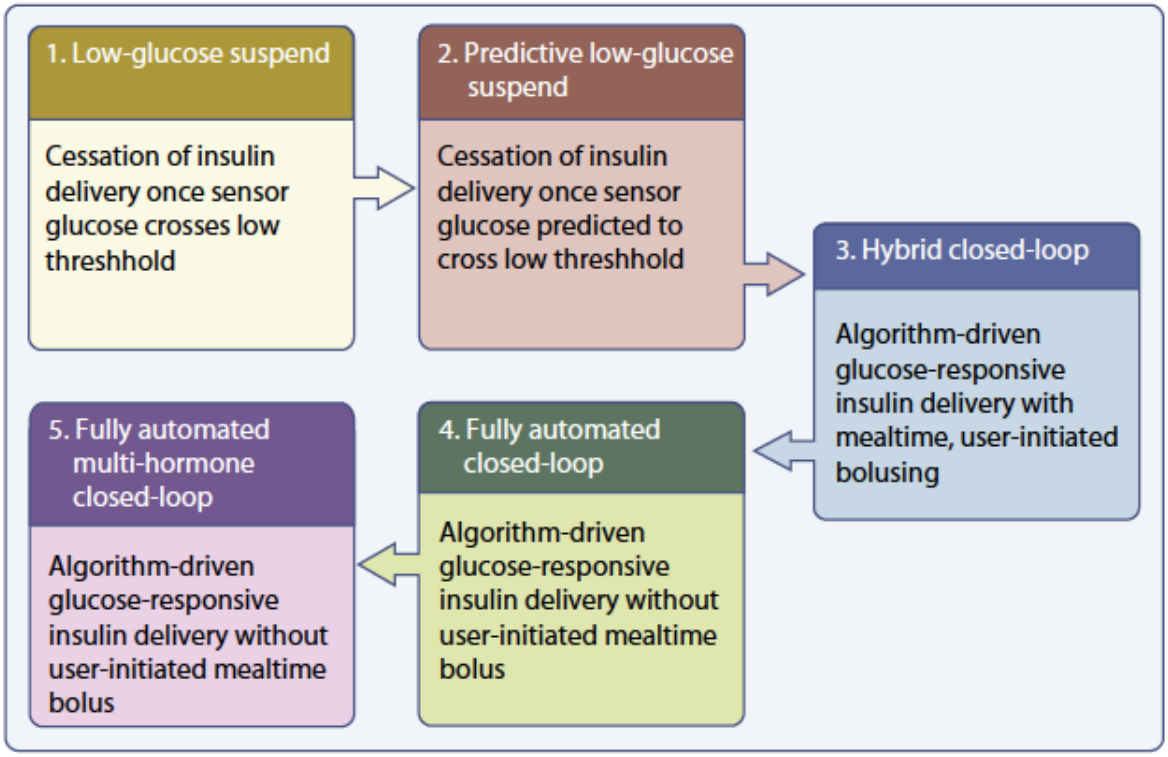
Another study evaluated changes in insulin delivery, carbohydrate intake and glycaemia throughout pregnancy in users of concurrent CGM and insulin pump use (but where the CGM does not interact with the insulin pump to automatically direct insulin dosing also known as open-loop insulin pump therapy or open-loop insulin delivery) (70). In 25 women, they described an average time spent in the pregnancy-specific target range of 59% ± 14% and despite intensified pump settings to manage gestational insulin resistance, users only achieved the 70% target time with glucose levels between 3.5-7.8mmol/L by 36 weeks' gestation. Along with the CONCEPTT data, where only one third of CGM users achieved the 70% pregnancy-specific CGM glucose target, these data indicate that more help is required to support women to achieve the tight targets associated with reduced obstetric and neonatal complications in type 1 diabetes pregnancy (57,71).

1.2.6 Hybrid closed-loop systems

More recently, there has been an increase in the development and use of closed-loop systems. The concept of closed-loop systems has been evolving over the last 50 years however, older generation components (continuous glucose monitors and insulin pumps) were unwearable and cumbersome, and continuous glucose monitors were not reliable or accurate enough to guide insulin dosing (72). The hybrid closed-loop system is one stage in a spectrum of glucose-responsive insulin delivery systems. The earliest glucose-responsive insulin delivery systems

suspended insulin delivery when glucose levels dropped below a certain threshold, before evolving to systems which were able to predict glucose levels trajectories and suspend glucose delivery when predicted to fall below specified thresholds (73,74). The addition of glucagon along with insulin to closed loop systems to form a dual hormone system may further protect against hypoglycaemia by mimicking the physiological secretion of glucagon when blood glucose levels drop. However poor stability of glucagon formulations, and the requirement for the user to wear two separate pumps has limited their widespread applicability (72,75). Furthermore, users of current single hormone systems are now achieving euglycaemia with such low hypoglycaemia rates that these limitations are unlikely to outweigh any potential benefits with respect to further reducing hypoglycaemia rates.

Figure 1.7 Key developmental milestones towards an artificial pancreas
(adapted from Boughton & Hovorka 2020) (72)



Current iterations of closed-loop systems comprise of 3 components:

(i) real time-CGM

(ii) an algorithm which calculates recommend insulin doses based on current CGM glucose levels and predicted CGM trends and trajectories

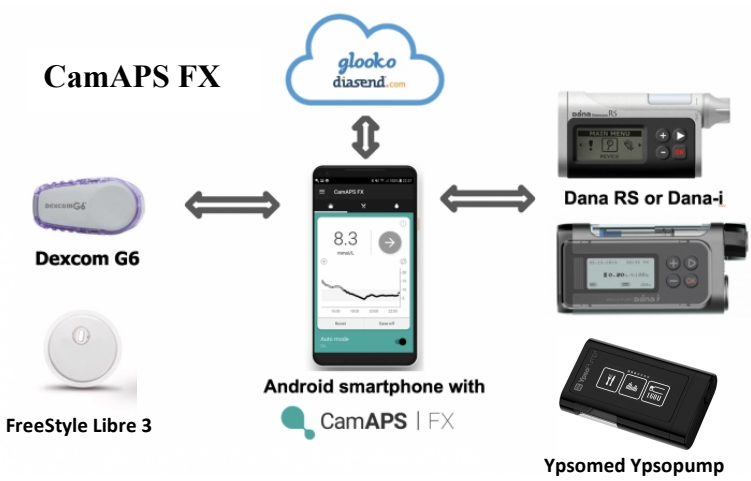
(iii) an insulin pump which delivers communicated insulin doses

This can be referred to as a hybrid system as users are still required to administer bolus insulin for meals (72). Given the glucose-responsive and predictive elements of the hybrid closed-loop algorithms as in-built safety mechanisms, these systems have the potential to improve on traditional insulin pumps by facilitating achievement of time in range targets whilst still preventing hypoglycaemia.

There are currently four commercially available hybrid closed-loop systems in the UK: Medtronic MiniMed 780G; Tandem Control IQ, Omnipod 5 and CamAPS FX. For the Medtronic, Omnipod and Tandem systems, the algorithm is within the pump software, whereas the CamAPS FX algorithm is a standalone smartphone application that users can download and connect via Bluetooth with different insulin pumps and CGM systems. The Omnipod 5 system is currently the only system involving a patch pump.

Table 1.3 Current commercially available hybrid closed-loop systems in the UK (Manufacturer in brackets)

Hybrid closed-loop system	Hybrid closed-loop algorithm form	Compatible insulin pump	Compatible CGM system
CamAPS FX (CamDiab)	Android smartphone application	Ypsopump (Ypsomed) OR Dana i (Sooil) OR Dana RS (Sooil)	Freestyle Libre3 (Abbott) OR Dexcom G6 (Dexcom)
Medtronic MiniMed 780G (Medtronic)	Pump software	780G (Medtronic)	Simplera (Medtronic)
Control IQ (Tandem Diabetes Care)	Pump software	T-slim (Tandem Diabetes Care)	Dexcom G6 (Dexcom) OR Dexcom G7 (Dexcom)
Omnipod 5 (Insulet)	Pump software	Omnipod (Insulet)	Dexcom G6 (Dexcom) OR Freestyle Libre2 Plus (Abbott)



As well as the commercially available systems, there are also D.I.Y. “self-built” artificial pancreas systems where insulin-dosing algorithms have been coded by groups (often including individuals with type 1 diabetes) and interface with existing insulin pump technology. This community was born out of the frustration of the slow progress of medical devices development (#wearenotwaiting). These algorithms are freely shared and available as open-source software or coding and are unlicensed with users taking responsibility for their use. There are currently three of these systems: AndroidAPS, OpenAPS and Loop with an ever growing community of users with type 1 diabetes who support and educate each other and healthcare professionals of their use (76,77).

Outside of pregnancy, commercial hybrid closed-loop systems have been developed and evaluated for efficacy and safety starting with highly supervised studies within a research facility of short duration (overnight or 24 hours) before progressing to larger and longer duration trials in home and outpatient settings. A meta-analysis of 40 studies assessing both single and dual hormone closed loop systems in a wide range of settings, from a diabetes camp or guest house to home settings, found that with closed-loop use, time spent in non-pregnancy target range (3.9-10.0mmol/L) was higher overnight (by 15%) and over 24 hours (10%) (78). They also were consistent with respect to safety with a reduction of 20 mins per 24 hours of time spent below 3.9mmol/L.

More recently there have been a huge increase in studies examining the use of hybrid closed-loop systems in both adult and paediatric populations. The use of hybrid closed-loop systems has rapidly become more widespread as studies consistently report efficacy in helping users meet glycaemic targets and for reducing the mental burden of diabetes self-management (79–82).

1.2.7 Use of hybrid closed-loop systems in pregnancy

In contrast to outside of pregnancy, maternal glycaemia is more complex due to the changes and challenges of advancing gestation: increases in insulin resistance and prolonged time to peak insulin action during the second and third trimesters, and exaggerated day to day variation (17,18,27–29). These challenges, unique to managing glycaemia in pregnancy, highlight the need for insulin therapies that are specifically designed to appropriately and

safely adjust for these gestational changes in order to help users achieve the tighter pregnancy glycaemic targets.

Only one of the four commercially available hybrid closed-loop systems used in the UK is currently licensed for use in pregnancy (CamAPS FX, CamDiab, Cambridge, United Kingdom). This system was developed and refined over four pilot closed-loop systems in pregnancy (CLIP) studies. These studies have provided the evidence base for the **A**utomated **I**nsulin **D**elivery **A**mong **P**regnant women with **Type 1 diabetes** (AiDAPT) randomised clinical trial (https://clinicaltrials.gov/ct2/show/NCT04938557) (83). The aim of the AiDAPT trial was to assess the efficacy of the CamAPS FX hybrid closed-loop system compared to CGM and usual insulin therapy during pregnancy (16 weeks until delivery) in real world NHS settings and the results of which will be reported and discussed in the following chapters of this thesis. There have since been other studies that have been reported and published following the AiDAPT trial which will be covered and discussed contemporaneously in the relevant chapters.

The first two closed loop in pregnancy studies: CLIP_01 and CLIP_02 were proof of concept studies performed in a carefully supervised clinical research setting. CLIP_01 sought to assess three things crucial to the safe use of hybrid closed-loop in pregnancy. Firstly, the accuracy of CGM in pregnancy, secondly the ability of the hybrid closed-loop algorithm to adjust basal insulin at early and late gestations and finally the safety and ability of the algorithm to cope with high carbohydrate meals (84). These meals were an 80 gram carbohydrate evening meal of pasta and a 60 gram carbohydrate breakfast of orange juice and toast with jam, which was more carbohydrate than most women with type 1 diabetes would usually eat for meals. Paired plasma and CGM glucose levels were examined, and authors demonstrated clinically acceptable CGM values with no overcorrection errors or unsafe control from the algorithm. Overnight, the algorithm performed safely to adjust insulin delivery at both early and late gestations with no episodes of symptomatic hypoglycaemia. Finally, in response to high carbohydrate meals, there was no difference between pre- and post-prandial glycaemia in either early or late pregnancy, demonstrating safe control of the algorithm in conjunction with user directed prandial boluses.

CLIP_02 tested the hybrid closed-loop system against conventional insulin pumps in a randomised cross-over design study in response to a series of “challenges” of normal

activities of daily living (85). Women used hybrid closed-loop therapy and conventional insulin pump therapy during pregnancy for 24 hours at 19- and 23-weeks' gestation. During the 24 hours, challenges to the system such as exercise, carbohydrate-rich meals and snacks were performed. Again these challenges were designed to be an exaggerated version of a "typical" activity of daily living to ensure the system could cope with these extreme challenges and hence cope well with unsupervised normal living in the home setting. Women performed three 20 minute walks and two sessions of 50 minute brisk walking on a treadmill during the 24 hours. Snacks were given pre-exercise depending on glucose levels. Overall, CLIP_02 demonstrated comparable time in pregnancy-specific target glycaemic range between hybrid closed-loop and insulin pumps but less time hypoglycaemic when using hybrid closed-loop. In response to these amounts of physical activity, the hybrid closed-loop algorithm was unable to prevent exercise-related hypoglycaemia, however authors noted that even with dual-hormone closed-loop systems, exercise-related hypoglycaemia cannot always be countered especially in the event of rapidly falling glucose levels or increased insulin present.

CLIP_03 was the first study to assess the feasibility of overnight hybrid closed-loop system in the home setting (86). This was a phase II randomised cross-over study, meaning that women used each treatment modality (hybrid closed-loop therapy and open-loop insulin pump therapy) for four weeks separated by a 1-2 week washout period in between. During the open-loop insulin delivery phase, women still wore CGM and had access to their CGM glucose data, but it did not communicate with their insulin pump directly in order to automate insulin dosing without user input. The primary outcome assessed was overnight time in pregnancy-specific target range (3.5-7.8mmol/L), which was 75% when using hybrid closed-loop compared to 59% using open-loop insulin pump therapy. They had a lower mean glucose (6.6 vs. 7.4mmol/L) with no difference in the amount of time spent <3.5mmol/L. This increase in time in range by 72 minutes a night in hybrid closed-loop compared to open-loop insulin pump therapy in an unsupervised home setting demonstrated a real potential to change clinical care in the effort to achieve >70% time in range with tight pregnancy targets and reduce adverse obstetric and neonatal outcomes.

CLIP_04 used the same randomised cross-over study design to evaluate both day and night use of hybrid closed-loop over 4 weeks in a broad population of women (87). Unlike previous CLIP studies, the majority of these women were new to technology (80% sensor-

naïve and 50% pump-naïve) and more than 50% of women had booking HbA1c >58mmol/mol (cf. NICE threshold of 48mmol/mol for risk stratification). Achieving target glycaemia during the day is more challenging due to meals, snacks and activity and the contribution of user directed prandial boluses to help manage glycaemia. Despite these challenges, CLIP_04 demonstrated comparable time spent in the pregnancy-specific target range when using hybrid closed-loop and open-loop insulin pump therapy, however importantly, women experienced less hypoglycaemia when using hybrid closed-loop therapy. Time spent <3.5mmol/L was 1.6% with hybrid closed-loop vs. 2.7% with open-loop insulin pump therapy and time <2.8mmol/L was 0.2% vs. 0.5%.

In both CLIP_03 and CLIP_04, study designs allowed for women to continue with hybrid closed-loop or either of the study devices (insulin pump or CGM) in combination or independently following completion of the two crossover arms until the end of their pregnancies (or 6 weeks postpartum in CLIP_04) (86–88). This allowed for evaluation of feasibility of the hybrid closed-loop system to be used continuously throughout pregnancy including following maternal corticosteroid administration, labour, delivery and immediate postpartum. The majority of women participating (30/32) chose to continue with hybrid closed-loop, a reflection of acceptability of this system to women. Furthermore, time spent in target range (3.5 - 7.8mmol/L) was maintained at 70% throughout pregnancy, in both women who had switched from insulin pumps and multiple daily injections. 27 out of the 32 participants used the hybrid closed-loop system during labour, delivery and immediate post-partum. The hybrid closed-loop system also performed well during vaginal, elective and emergency caesarean sections. These women achieved >80% time in the relevant target ranges during labour and delivery (3.5 - 7.8mmol/mol) and the first 48 hours postpartum (3.9 - 10.0mmol/mol).

Together these studies show promise in an insulin therapy and delivery system that may be able to adequately and safely adjust for and accommodate the gestational challenges of managing type 1 diabetes throughout pregnancy.

1.3 Aims of the thesis

This aims of this thesis are:

1. To evaluate the clinical efficacy and safety of CamAPS FX hybrid closed-loop therapy compared with continuous glucose monitoring and standard insulin therapy during pregnancy
2. To capture women's lived experience of managing type 1 diabetes during pregnancy and assess the acceptability of using hybrid closed-loop therapy in type 1 diabetes pregnancy
3. To capture healthcare professionals' experience of supporting hybrid closed-loop use in type 1 diabetes pregnancy and highlight potential challenges to a national roll out of hybrid closed-loop (if proven clinically effective)
4. To evaluate the clinical efficacy and safety of CamAPS FX hybrid closed-loop therapy compared with CGM and standard insulin therapy during the first six months' postpartum
5. To capture women's lived experience of managing type 1 diabetes after delivery and acceptability of using hybrid closed-loop therapy in the immediate postpartum period

Chapter 2: Biomedical results of the AiDAPT trial

2.1 Chapter Introduction

Chapter 1 described the additional challenges of managing type 1 diabetes in pregnancy and described and outlined the evidence for recent advances in diabetes therapies and technology. This chapter presents the main biomedical data and analyses from the AiDAPT (**A**utomated **I**nsulin **D**elivery **A**mong **P**regnant women with **T**ype 1 diabetes, ISRCTN56898625) randomised controlled trial comparing hybrid closed-loop therapy with standard insulin therapy alongside continuous glucose monitoring during type 1 diabetes pregnancy.

2.2 Chapter Summary

Background: Type 1 diabetes in pregnancy is associated with an increased risk of complications for both the mother and fetus. It is well established that maternal glycaemia is a major modifiable risk factor in reducing these risks. However, despite many advances in insulin therapy and diabetes technologies such as continuous glucose monitoring, rates of large for gestational age babies, preterm births and neonatal intensive care unit (NICU) admissions remain high. Outside of pregnancy, hybrid closed-loop therapy is associated with improved glycaemia for adults and children with type 1 diabetes. However whilst hybrid closed-loop therapy shows promise for managing type 1 diabetes during pregnancy, its clinical efficacy is unclear.

Methods: In this multicentre parallel-group controlled trial, pregnant women with type 1 diabetes and early pregnancy ≥HbA1c 48mmol/mol at nine United Kingdom sites were randomised to standard insulin therapy with continuous glucose monitoring (control group) or to hybrid closed-loop therapy (intervention group). The primary outcome was the between-treatment difference in percentage of time spent with CGM sensor glucose measurements in the pregnancy-specific target range (3.5-7.8mmol/L) from 16 weeks' gestation until delivery. Analyses were performed according to intention-to-treat principles. Key secondary outcomes included percentage of time spent hyperglycaemic (>7.8mmol/L), overnight percentage time in range, HbA1c, and maternal safety events (severe hypoglycaemia, diabetic ketoacidosis).

Results: 124 participants with a mean ± SD age of 31.1 ± 5.3 years and early pregnancy baseline HbA1c of 61 ± 13mmol/mol were randomised. The mean (± SD) percentage of time with maternal glucose levels within the pregnancy-specific target range (3.5 - 7.8mmol/L) during pregnancy was 68.2 ± 10.5% for the hybrid closed-loop and 55.6 ± 12.5% for the

control group: mean adjusted difference, 10.5% (95% confidence interval [CI], 7.0% to 14.0%; $p < 0.001$). Results were consistent in secondary outcomes, with significantly less time spent with glucose levels above the hyperglycaemic threshold of 7.8mmol/L (-10.2%, 95% CI -13.8% to – 6.6%); higher overnight time in range (12.3%, 95% CI 8.3% to 16.2%); and lower HbA1c; (-3.4mmol/mol, 95% CI -5.5, -1.3mmol/mol) all favouring the hybrid closed-loop intervention group. Time spent hypoglycaemic <3.5mmol/L was low, around 2% in both groups. There were no unanticipated safety problems associated with hybrid closed-loop use during pregnancy: six versus five severe hypoglycaemia episodes and one diabetic ketoacidosis per group.

Conclusions: Hybrid closed-loop therapy significantly improved maternal glycaemia during pregnancy complicated by type 1 diabetes over and above the level that can be achieved with CGM and standard insulin therapy. These data support a recommendation that hybrid closed-loop therapy should be offered to all pregnant women with type 1 diabetes

2.3 Background

2.3.1 Managing type 1 diabetes in pregnancy

One in two babies born to women with type 1 diabetes experience complications, most commonly large for gestational age birthweight, preterm births and neonatal care unit admissions (6,89). Maternal antenatal hyperglycaemia is the major risk factor for these complications, with the highest risk among women entering pregnancy with above-target HbA1c levels. Therefore the UK NICE Diabetes in Pregnancy guideline recommends that women with diabetes who are planning a pregnancy aim to keep their HbA1c level below 48 mmol/mol, if this is achievable without causing problematic hypoglycaemia (34). Cohort studies and, more recently, randomised trials have demonstrated that improved maternal glycaemia reduces the risk of obstetric and neonatal complications and improves pregnancy outcomes (6,8,57,89). However, despite improvements in insulin therapy, continuous glucose monitoring, and high motivation for diabetes self-management, attainment of the pregnancy-specific glucose targets of 3.5-7.8mmol/L as compared to 3.9 -10.0mmol/L outside of pregnancy, remains elusive for most women (52,70,71,89).

During pregnancy, challenges such as altered eating patterns, nausea and vomiting of pregnancy, marked gestational variations in insulin sensitivity and stringent pregnancy glucose targets complicate diabetes self-management (17,18,28). Striving for these lower pregnancy glucose levels also increases the risk of severe hypoglycaemia, a leading cause of maternal morbidity and mortality, whilst hyperglycaemia (>7.8mmol/L) is associated with fetal pancreatic hyperinsulinaemia and associated neonatal complications (8,13,90). Outside of pregnancy, use of hybrid closed-loop therapy is associated with improved glycaemia in both children and adults, but whether they can help achieve the more stringent glucose targets required for optimal pregnancy outcomes is unknown (91).

2.3.2 The CamAPS FX hybrid closed-loop system

The CamAPS FX hybrid closed-loop system is an android smartphone application that runs the Cambridge model predictive control algorithm. The android phone then communicates with both an insulin pump and CGM system by Bluetooth. The system algorithm calculates a glucose-responsive basal rate in response to continuous glucose monitor levels. This basal rate is delivered as extended boluses by the insulin pump every 8-12 minutes when in Auto Mode. The algorithm calculations are directed by a “personal glucose target”, which can be

set from 4.4mmol/L to 11.0mmol/L and a default level of 5.8mmol/L is recommended outside pregnancy. In case of technical glitches or unintended exits from Auto Mode (including if glucose data were not available for >30 minutes, for example during sensor warm up or loss of Bluetooth connection between the smartphone and CGM or loss of power of the smartphone), the insulin pump would revert to the individuals pre-programmed basal profile (Manual Mode).

With CamAPS FX, the user is also able to influence the basal insulin delivery and "aggressiveness" of algorithm calculations to allow the system to respond to other factors that can affect maternal glycaemia such as physical activity and concurrent illness by using two sister functions: "boost" and "ease off". Boost increases insulin delivery by up to 35% and is typically used during concurrent illness or to help resolve unexpected hyperglycaemia (including supporting inadequate mealtime boluses and prandial hyperglycaemia). "Ease-off" temporarily raises the personal glucose target, so insulin delivery will be reduced or paused at a higher glucose level and thereby decreasing insulin delivery overall for the duration the setting is active. Crucially, these functions are still glucose-responsive. In the case of "boost", if the CGM glucose readings are below the target range or a downward trend is predicted, the algorithm will ignore the "boost" function until the CGM glucose readings are within range or trending upwards. The reverse is true for "ease off" and hybrid closed-loop users are typically advised to use these functions for 2-4 hours at a time.

Meals are bolused for using the in-built bolus calculator into which the user inputs their insulin-to-carbohydrate ratios and insulin sensitivity factors (also known as correction factors). As with standard pump or multiple daily insulin injection users, hybrid closed-loop users are recommended to continue bolusing 10-15 minutes prior to their meal in order to time maximal insulin absorption and action with the peak of carbohydrate absorption.

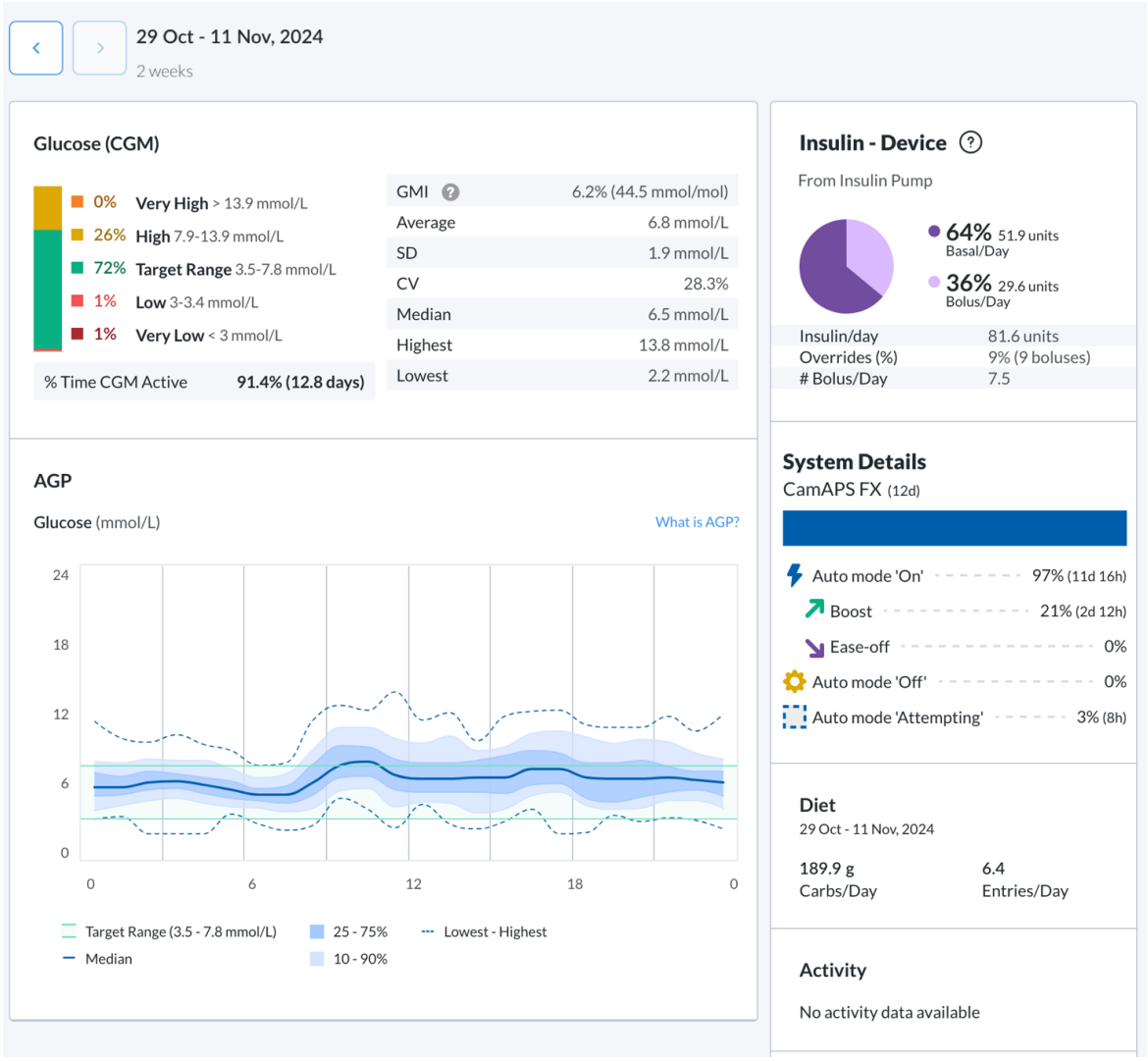
A further way the user can interact with the system is to notify the system of carbohydrate intake that they do not wish to bolus for. This could be in the form of "hypo treatment" or "meal / snack" if the user usually has a snack before physical activity to reduce the hypoglycaemia risk. By notifying the system of this carbohydrate intake, subsequent CGM glucose rises are managed differently as the algorithm takes into account this additional information from the user.

Lastly, users are also able to give manual correction doses without needing to "trick" the system by inputting "fake carbs" i.e. telling the system they are having carbohydrate intake in order to give themselves more insulin. This is useful if they have had a recent insulin pump set failure (i.e. an issue with the pump cannula meant that they did not receive the insulin the pump thought they did) or other circumstances where they may need to rapidly give more insulin rather than rely on the inbuilt corrective features (automated basal delivery / "boost").

Similar to standalone CGM, both CGM and insulin data and pump and hybrid closed-loop settings can be assimilated, analysed and displayed by reporting software. The CamAPS FX system has in-built reporting software but also syncs with the Diasend / Glooko diabetes data platform. Data most commonly reviewed is the ambulatory glucose profile, pump and hybrid closed-loop settings and insulin delivery and doses (Figure 2.1).

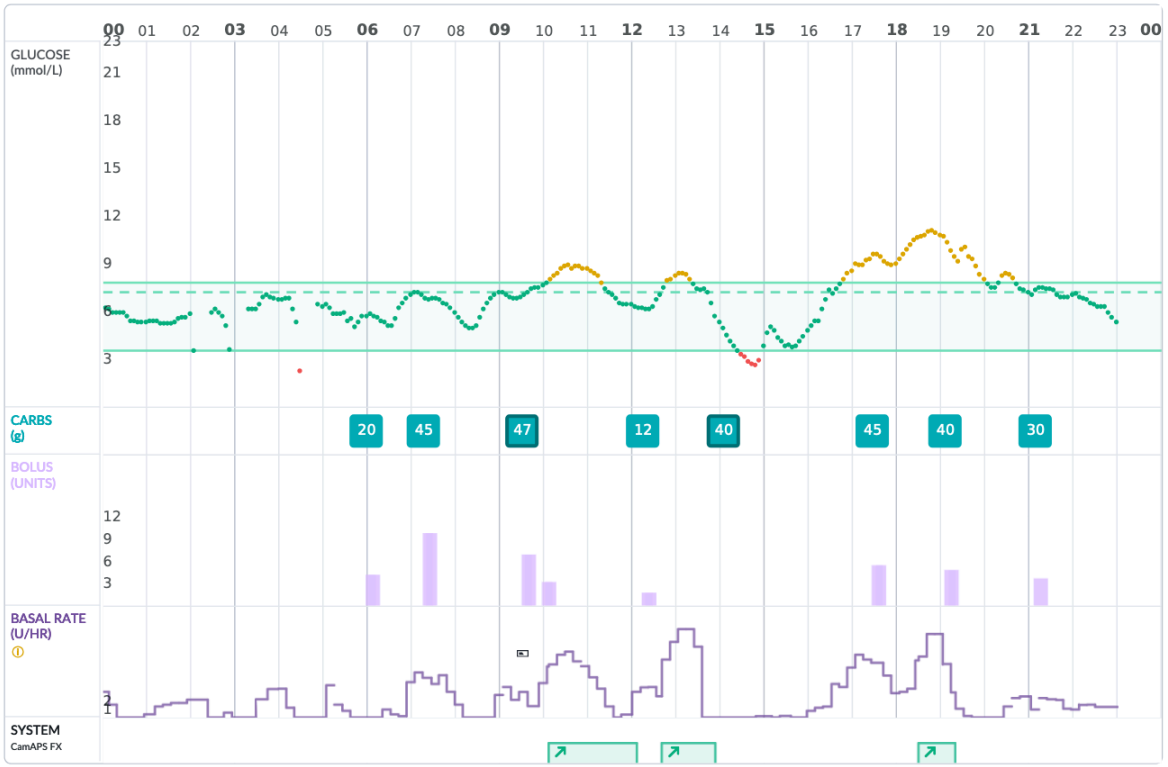
Figure 2.1 An example of hybrid closed-loop summary data displayed by diabetes reporting software

A. CGM time in range metrics, ambulatory glucose profile and system data
Summary CGM data customised for pregnancy-specific time in range targets



B. Single daily graph

Single daily graph demonstrating varying basal rate as per hybrid closed-loop algorithm (purple line); continuous glycaemic data (green, orange and red dots); boluses including prandial boluses (Carbohydrate amount shown in teal carbohydrate box with insulin bolus units in purple bolus bar). Other data reported and described as per report legend (bottom left).



Pump Boluses

Bolus Table only shows the first 10 bolus events for the day.

	1 06:06	2 07:24	3 09:38	4 10:06	5 12:22	6 14:12	7 14:31	8 14:37	9 17:35	10 19:13
Bolus Delivered	4.4	10	7.1	3.3	2	0	0	0	5.6	5
Suggested	4.4	10	7.1	3.3	2	0	0	0	5.6	5
MEAL	4.4	10	7.1	3.3	2	-	-	-	5.6	5
Correction	-	-	-	-	-	-	-	-	-	-
Insulin On Board	-	-	-	-	-	-	-	-	-	-
Initial	-	-	-	-	-	-	-	-	-	-
Extended	-	-	-	-	-	-	-	-	-	-
Duration	-	-	-	-	-	-	-	-	-	-
Carbs	20	45	32	15	12	15	15	10	45	40

System (CamAPS FX)
- Boost

Types of Readings
- Below Target
- In Range
- Above Target
- CGM Readings
- Carbs
- Multiple carb entries

Glucose
- Before Meal Upper Limit: **7.2**
- After Meal Upper Limit: **7.8**
- Normal Glucose: **3.5**
- Target Range: **3.5 - 7.8**

Insulin Dose
- Bolus Delivered

Basal
- Reservoir Fill
- Basal Rate
- The basal segment in progress at the time of download is not displayed

Statistics

	10/NOV	29/OCT - 11/NOV
BG statistics		
Av. BG	0	0
Median BG	0	0
BG readings	0	0
Av. CGM	6.8	6.8
Median CGM	6.8	6.5
% CGM very high	0%	0%
% CGM High	25%	26%
% CGM Target Range	72%	72%
% CGM Low	1%	1%
% CGM Very Low	2%	1%
Insulin – Device		
Bolus	41.2 u	29.6 u
Basal	57.3 u	51.9 u
Total insulin	98.5 u	81.6 u
# of boluses	12	7.5
Av. Bolus	3.4 u	4 u
# Corr. bolus	0% (0)	12% (0.9)

At the time of this study, CamAPS FX is the only hybrid closed-loop system that has a license for use in type 1 diabetes pregnancy in the UK. Its development for use in and adaptability for pregnancy has been developed through four pilot studies, including two randomised controlled trials, summarised in Chapter 1 of this thesis (84–87). In addition, there were multiple case reports and small case series of the off-label use of other commercially available hybrid closed-loop systems in pregnancy with small numbers of women (Table 2.1). These studies with small numbers of participants and short duration of hybrid closed-loop use were extremely limited in size and scope. They lacked statistical power to determine the clinical efficacy of hybrid closed-loop use in pregnancy. Furthermore, as these other systems were designed and developed to optimise insulin delivery to achieve non-pregnancy targets of 3.9-10.0mmol/L. Additional guidance was needed for women entering pregnancy on how these algorithms and systems could be influenced and manipulated in order to improve their ability to aim for the lower pregnancy targets (92).

Additionally, there were three studies in the development of a pregnancy-specific zone model predictive controller (zone-MPC) based closed-loop control, referred to as CLC-P (93–95). The first tested the system *in silico* experimentation using computer-based simulation, providing proof of concept data. The second examined its performance on eleven pregnant women in a 2-day supervised outpatient study, showing satisfactory performance. The third study included ten pregnant participants and examined its use in supervised home settings from 23.7 ± 3.5 weeks' gestation until delivery. This study demonstrated an improvement in time in the pregnancy-specific target range of 14.1% (3.4 hours per day) compared to baseline, however the algorithm is still in the experimental phase of development.

The AIDAPT trial examined whether the CamAPS FX hybrid closed-loop system started before 16 weeks' gestation would improve maternal glucose levels during pregnancy complicated by type 1 diabetes.

Table 2.1 Studies evaluating off-label use of commercially available hybrid closed-loop systems in type 1 pregnancy (published prior to October 2023)

Study*	**Number of participants[α]**	**HCL system**	**Timing of HCL automode initiation**
Polsky et al 2020 (96)	N = 3	Medtronic Minimed 670G	One started automode at 18 weeks. The other two used HCL throughout pregnancy but inconsistent use of automode
Guzmán Gómez et al 2021 (97)	N = 1	Medtronic Minimed 670G	Switched to Minimed 670G at 30 weeks' gestation and started automode at 32 weeks
Moreno-Fernández et al 2021 (98)	N = 1	Medtronic Minimed 670G	Started automode at 16 weeks
Munda et al 2022 (99)	N = 6	Medtronic Minimed 780G	Three started pre-pregnancy and three started at the beginning of pregnancy
Vambergue et al 2022 (100)	N = 1	Diabeloop	Started pre-pregnancy
Wang et al 2023 (101)	N = 4	Tandem Control IQ	All started pre-pregnancy
Albert et al 2023 (102)	N = 6	Medtronic Minimed 780G	Four started pre-pregnancy Two started during the first trimester
Dodesini et al 2023 (103)	N = 8	Medtronic Minimed 780G	Five started pre-pregnancy Three started between 8 and 13 weeks' gestation
Baagar et al 2023 (104)	N = 2	Medtronic Minimed 670g / 780G	One started pre-pregnancy One switched from Minimed 670G (started pre-pregnancy) to Minimed 780G at 23 weeks' gestation
Guibert et al 2023 (105)	N = 13	Medtronic Minimed 780G	All started pre-pregnancy

[α] HCL = hybrid closed-loop therapy

2.4 Methods

2.4.1 Study design

In this open-label, multicentre, randomised controlled trial participants were recruited from nine National Health Service sites in England, Scotland and Northern Ireland. Participants were randomised to receive automated insulin delivery (hybrid closed-loop intervention group) or to continue standard insulin therapy (via multiple daily injections or insulin pump) together with CGM (control group).

Approval of the trial protocol, which is available in the Appendix of this thesis, was received by the relevant Health Research (Research Ethics Committee 18/EE/0084), and Regulatory Authority (Medicines and Healthcare Products Regulatory Agency). Oversight was provided by an independent Trial Steering Committee, with individual members and chairperson approved and appointed by the trial funder, National Institute for Health and Care Research (NIHR). Safety aspects were reviewed by an independent data monitoring committee, also approved and appointed by the trial funder. The Trial Management Committee was responsible for the design of the trial and the decision to submit the manuscript for publication. Details of the trial protocol are published and registered at ISRCTN 56898625 (83).

The Norwich Clinical Trials Unit (Norwich, UK) was responsible for the UK Health Research Authority and Medicines and Healthcare Products Regulatory Agency regulatory approvals, day to day trial management, data monitoring and safety outcomes. The Jaeb Center for Health Research (Tampa, Florida, USA) was responsible for the randomisation scheme, trial database, data validation, and detailed statistical analyses. Trial funding was provided by the Efficacy Mechanism and Evaluation Programme (EME Project: 16/35/01), which is jointly funded by the Medical Research Council and NIHR. Additional support for the Jaeb Center for Health Research clinical trial unit input was provided by the Juvenile Diabetes Research Foundation (JDRF) with continuous glucose monitoring devices provided by Dexcom at a discounted research price. Representatives from Dexcom and the NIHR received a copy of the manuscript before submission without any input on the content or any agreements concerning data confidentiality or publication rights between the companies the authors or their institutions. The statistical analysis plan is included with the protocol in the Appendix of this thesis.

2.4.2 Trial participants

Pregnant women, aged between 18 and 45 years, with at least 12 months' duration of type 1 diabetes were recruited as soon as possible after ultrasound confirmation of a viable pregnancy and before 14 weeks' gestation. Participants using intensive insulin therapy (multiple daily injections or insulin pump) were eligible if they had a HbA1c of ≥48mmol/mol during early pregnancy and ≤86mmol/mol at randomisation.

Exclusion Criteria

1. Non-type 1 diabetes
2. Other physical or psychological disease which is likely to interfere with the normal conduct and interpretation of the study results, as per investigator judgement
3. Current treatment with drugs known to interfere with glucose metabolism (e.g. high dose corticosteroids)
4. Known or suspected insulin allergy
5. Advanced nephropathy (eGFR <45mL/min/1.73m^2), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as per investigator judgement
6. Target glycaemia or very high HbA1c i.e. first antenatal HbA1c <48mmol/mol or HbA1c >86mmol/mol. Those with HbA1c >86 mmol/mol may participate if they achieve HbA1c ≤86mmol/mol before randomisation.
7. Total daily insulin dose ≥1.5 units/kg
8. Severe visual or hearing impairment
9. Unable to speak and understand English

2.4.3 Trial procedures

Screening, recruitment and run-in period

Participants were screened for eligibility by local clinic teams. All participants provided written informed consent and baseline data including past medical, diabetes and obstetric history, current diabetes management alongside a brief physical examination (blood pressure, height and weight measurements) were collected. Participants were then supplied with a masked study CGM to ensure the device was tolerated and provide a baseline assessment of glycaemia (at least 96 hours of sensor glucose values, including 24 hours overnight).

They were also asked to complete the following validated questionnaires as applicable; Euroqol Five Dimensions Health-Related Quality of Life Questionnaire (EQ-5D-5L) , Diabetes Distress Scale, Hypoglycaemia Fear Survey II (worry scale only), and Pittsburgh Sleep Quality Index (106–109). The relevant permissions were sought and received for all questionnaires during study protocol development and examples of these questionnaires are included in the Appendix of this thesis. HbA1c measurements were performed at each site, using an International Federation of Clinical Chemistry Laboratory Medicine–aligned methodology.

Randomisation

Eligible participants underwent randomisation 1-2 weeks after recruitment and before 16 weeks' gestation. Treatments were allocated in a 1:1 ratio via a web-based system that used a computer-generated randomisation list with permuted block sizes of 2 and 4 and stratification by clinical site.

2.4.4 Treatments

Hybrid closed-loop system

The version of the CamAPS FX system used in this study comprised of three components (Figure 2.2):

- CamAPS FX application (version 0.3.71, CamDiab, Cambridge, UK) hosted on an unlocked android smartphone, Galaxy S8-12 (Samsung, Suwon-si, South Korea).
- Dana Diabecare RS insulin pump (Sooil, Seoul, South Korea)
- Dexcom G6 CGM (Dexcom, San Diego, USA)

Figure 2.2 CamAPS FX hybrid closed-loop system used in the AiDAPT trial
Photo credit: Julia Ware (University of Cambridge, Cambridge, UK)

When starting on CamAPS FX the participant's weight and total daily insulin dose were provided to the system and their insulin-to-carbohydrate ratios and insulin sensitivity factors (correction factors) are programmed into the pump bolus calculator.

To mitigate for potential technical glitches and ensure ongoing insulin delivery, a pre-programmed basal profile was set for every hybrid closed-loop user on the insulin pump as it would revert to this profile (Manual Mode) in the event that Auto Mode not being available (for example loss of smartphone or loss of Bluetooth connection between CGM and smartphone). If already a pump user, their previous pre-programmed basal rate was programmed into the insulin pump. For those previously on multiple daily injections, their total daily insulin dose was standardised to 70 ± 10% of their injection total daily dose and a pre-programmed flat basal rate of half their injection total daily insulin dose split evenly over 24 hours. The recommended personal glucose target during pregnancy was 5.5mmol/L during the first trimester then 4.5-5.0mmol/L from the second and third trimesters (or as soon as risk of hypo was low) in order to achieve pregnancy CGM targets: at least 70% time in range, between 3.5-7.8mmol/L (16 hours 48 minutes a day), with no more than 25% time >7.8mmol/L (6 hours 12 minutes a day) and less than 4% time below 3.5mmol/L (1 hour a day). Participants were trained to use CamAPS FX by the research educator or by local teams.

Standard care group

Participants continued multiple daily injections or insulin pump therapy with insulin dose adjustment as directed by their local teams. Those not using Dexcom G6 CGM were trained and switched onto this system after randomisation for glucose monitoring. Local teams provided training on both CGM use and insulin dose adjustment.

Figure 2.3 Dexcom G6 CGM system used in the AiDAPT trial

1. Dexcom G6 sensor
2. Dexcom G6 sensor and transmitter
3. Receiving device: smartphone and Dexcom G6 receiver

Insulin dose adjustment

Participants in both groups were reviewed by their local clinical teams at 2-4 weekly intervals in accordance with national guidelines for management of type 1 diabetes during pregnancy. Healthcare teams and participants in both groups were given standardised information regarding pregnancy CGM targets, aiming for 70% time in the pregnancy-specific range (3.5-7.8mmol/L) with an emphasis on the expected increases in insulin doses during the second and third trimesters. Participants were encouraged to administer pre-meal insulin at least 15 minutes before eating during the first trimester, increasing to 30 ±10 mins in the second and third trimesters, in line with best practice guidelines.

Training resources for trial staff and participants

Ongoing training was available to all participants and trial staff in the form of online resources. CGM training modules and "Top Tips" patient education leaflets from the Association for British Clinical Diabetologists' Diabetes Technology Network were available to participants and staff. A further "Top Tips" leaflet for using the pump and hybrid closed-loop system was provided to intervention arm participants. In addition, CamDiab training webinars for both participants and trial staff were available from https://camdiab.cdep.org.uk/view/20/Webinars.htm. Copies of the "Top Tips" leaflets are included in the Appendix of this thesis.

Participant technical support

All participants had access to support from their study teams and Dexcom technical support in case of technical problems with their continuous glucose monitor devices or Bluetooth connectivity. Those randomised to hybrid closed-loop insulin delivery were also signposted to Advanced Therapeutics (UK suppliers of Sooil devices) in case of pump-related problems and had access to a telephone helpline to contact the research study team for any concerns about their hybrid closed-loop function and device connectivity.

2.4.5 Study visits

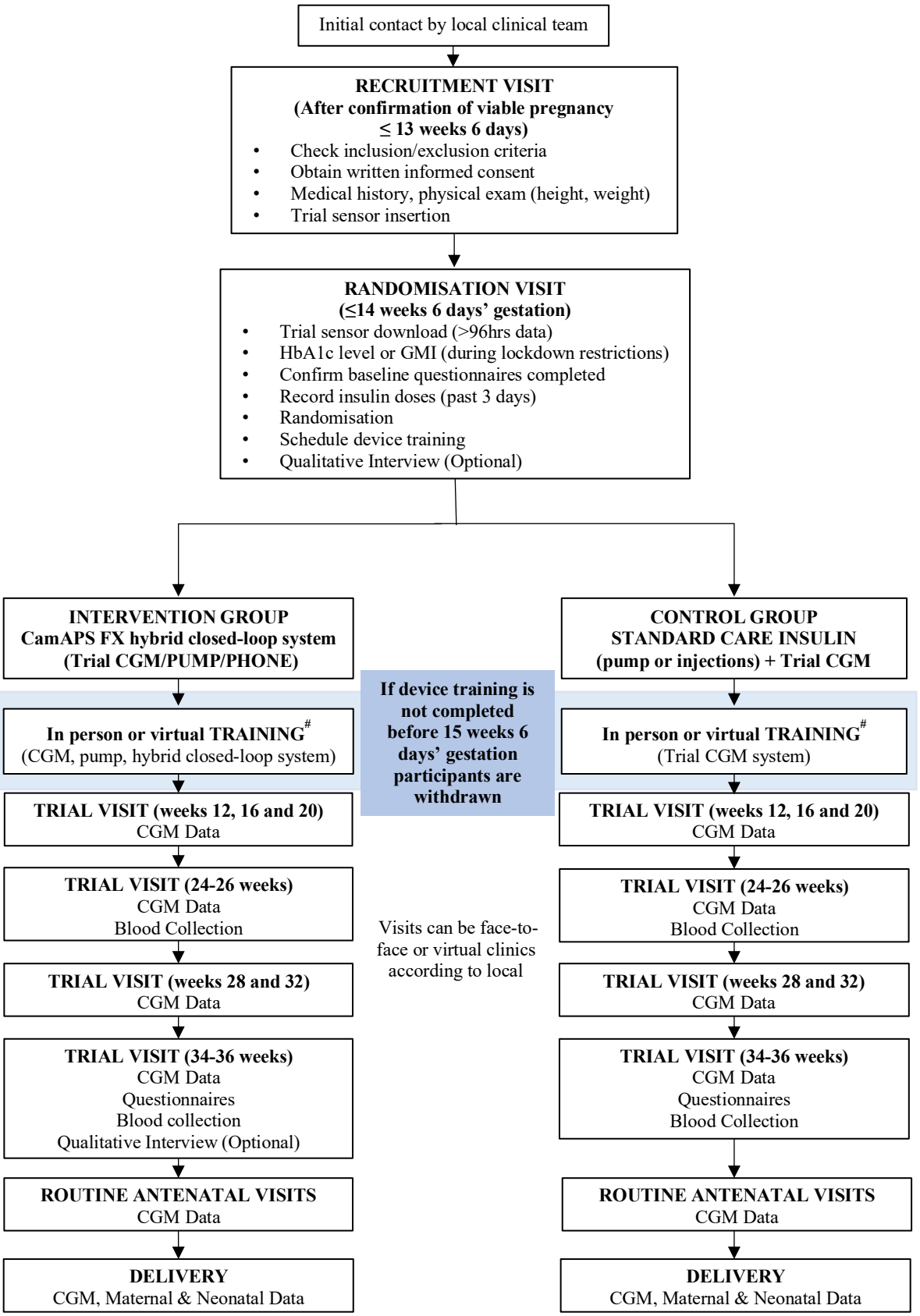
Study visits

After randomisation, study visits were scheduled to coincide with routine clinic visits to occur at least four-weekly from 12 to 36 weeks' gestation depending on gestation at randomisation (Figure 2.4). Additional visits and contacts occurred as clinically indicated. At each study visit, biomedical data were collected: maternal weight and blood pressure, insulin dose and type, details of device issues and adverse events. Participants were requested to repeat baseline questionnaires at 34-36 weeks and for intervention arm participants, an additional INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) questionnaire was also included (110). HbA1c levels were repeated where possible at 24-26 and 34-36 weeks' gestation. Obstetric input and ultrasound scans were performed at approximately 20, 28, 32 and 36 weeks' gestation as per routine clinical care. Any inpatient hospital admissions were also recorded. At delivery, data regarding obstetric and neonatal outcomes were collected.

Modifications to the study protocol

The COVID-19 pandemic led to changes in maternity service provision within the NHS, with increased clinical pressures among trial staff and restricted face-to-face visits and laboratory access. In order to maintain safety of participants and healthcare professionals and minimise staff burden, the use of glucose management indicator (GMI) estimates from participants already using intermittent or real-time CGM systems were allowed as part of inclusion criteria if a laboratory HbA1c level was unavailable and the option of virtual research study visits and device training via video-call or telephone were added to the study protocol.

Figure 2.4 Flow of participants through the study



#Virtual device training procedures and visits were implemented following the COVID-19 lockdown restrictions

2.4.6 Outcomes

The primary efficacy outcome was between-group difference in the percentage of time spent in the pregnancy target glucose range of 3.5-7.8mmol/L from 16 weeks' gestation until delivery. Key secondary outcomes were percentage of time spent above target (>7.8mmol/L), reflecting antenatal hyperglycaemia and percentage of overnight time in the target glucose range, more reflective of the 'steady-state' performance of the hybrid closed-loop system with less of the additional user impact required during meals and activity. A pre-specified subset of sensor glucose outcomes (mean glucose, percentage time spent in, above and below relevant thresholds, glycaemic variability, hypoglycaemic events) were calculated for overnight periods (23.00-07.00) and for each trimester. Additional secondary outcomes included HbA1c, insulin doses, and attainment of pregnancy International Consensus on Time in Range CGM targets (52).

Safety outcomes included the number of severe hypoglycaemia, diabetic ketoacidosis, and adverse device events. Adverse device events are defined as adverse events related to the use of an investigational medical device including user error. In this study, relation to the investigational medical device was further characterised to the corresponding contributing components i.e. the CGM sensor or connectivity, insulin pump connectivity or pump cannula set failures or the hybrid-closed loop algorithm itself.

Maternal and neonatal outcomes were documented at hospital discharge following delivery and included maternal gestational weight gain and hypertensive disorders, neonatal morbidity, NICU admissions and pregnancy loss including miscarriages, stillbirths and neonatal deaths. Qualitative outcomes included questionnaires as listed below and interviews with both study participants and trial staff.

Maternal glucose outcomes

1. The percentage of time spent with sensor glucose levels above (TAR) and below (TBR) target range (>7.8mmol/L and <3.5mmol/L), mean sensor glucose and glucose variability measures; glucose standard deviation (SD) and glucose coefficient of variation (CV)
2. The frequency and severity of hypoglycaemia episodes <3.5 mmol/L (mild) and <3.0 mmol/L (moderate) for more than 15 minutes duration

3. The International Consensus on Time in Range CGM targets; CGM glucose levels 3.5-7.8mmol/L >70% (16hr 48 min), >7.8mmol/L <25% (6hr), <3.5mmol/L <4% (1hr), and <3.0mmol/L <1% (15min)
4. Change in maternal HbA1c based on blood samples collected at baseline, 24-26 weeks, 34-36 weeks
5. CGM glucose levels during the first (<12 weeks 6 days gestation), second (13-27 weeks 6 days gestation) and third trimesters (28 weeks until delivery)
6. CGM glucose levels during 24-hours (midnight to midnight) and overnight time 23.00- 07.00hr

Maternal obstetric outcomes

1. Gestational weight gain
2. Maternal hypertensive disorders
3. Mode of delivery
4. Gestational age at delivery
5. Preterm delivery (<37 weeks)
6. Adverse events including pregnancy loss <24 weeks, stillbirth, neonatal death
7. Maternal hospital admissions and length of hospital stay

Neonatal outcomes

1. Neonatal morbidity including treatment for neonatal hypoglycaemia, neonatal jaundice and respiratory distress
2. Infant birth weight
   (customised birth weight percentile, incidence of large and small for gestational age)
3. Neonatal care unit admission >24 hours
4. Hospital length of stay (from delivery until hospital discharge), including re-admissions >24h within the first seven days from birth

Psychosocial outcomes

These analyses and results are reported in Chapter 3.

1. Questionnaires during early and late pregnancy: Euroqol Five Dimensions Health-Related Quality of Life Questionnaire (EQ-5D-5L); Diabetes Distress Scale; Hypoglycaemia Fear Survey II (worry scale only); and Pittsburgh Sleep Quality Index (106–109).

2. Questionnaires for intervention arm participants during late pregnancy: Insulin Delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) (110).
3. Qualitative interviews: both participants and trial staff.

2.4.7 Statistical analyses

It was calculated that 98 enrolled participants were needed to provide 90% power to detect a 10% absolute difference in the primary outcome (percentage of time spent in the pregnancy-specific target glucose range) from 16 weeks until delivery, based on a standard deviation of 15%, and a 2-sided type 1 error rate of 5%. The sample size was increased to 124 to allow for dropouts due to pregnancy losses and withdrawals from the study for other reasons.

Calculation of CGM-measured outcomes

Baseline: CGM variables were calculated based on data obtained in the run-in period prior to randomisation. Each recruited participant wore a study CGM sensor at home during run-in for up to ten days. At least 96 hours of CGM glucose values with 24 hours of glucose values during 23:00 – 07:00 were required for randomisation. To avoid large gaps in the data, CGM data in the 14 days prior to randomisation date was included, and if less than 96 hours of data was obtained, additional days were added one at a time until 96 hours or 28 days prior to randomisation were reached, whichever came first.

Follow up: For both hybrid closed-loop arm and control arm, CGM data from 16 weeks' gestation until delivery were used to calculate all CGM metrics for the intervention phase. If a participant miscarried or had a termination of pregnancy, CGM data until that day was included for calculating CGM metrics. A minimum of 96 hours of CGM data was required for the calculation, otherwise, values would have been considered missing and imputed in the analysis. CGM metrics were also calculated overnight, defined as 23:00 to 07:00, with a minimum of 24 hours of CGM data required during that time period.

CGM metrics were also calculated for each trimester, with a minimum of 24 hours of data required for the calculation. The first trimester is from the day after randomisation until 12 weeks 6 days' gestation, the second trimester is from 13 weeks until 27 weeks 6 days, and the third trimester is from 28 weeks until delivery.

HbA1c and insulin outcomes

HbA1c values were collected at baseline, 24 weeks, and 34 weeks' gestation. The analysis window for 24 weeks was 20 to <30 weeks' gestation, and the analysis window for 34 weeks was 30 weeks' gestation to delivery. If no HbA1c value was available in the window, GMI estimates were used instead (55). GMI was calculated from CGM data during 23 to <26 weeks' gestation and 33 to <36 weeks. Insulin data was recorded at study visits onto the database. Baseline insulin data came from the earliest study visit before 14 weeks. Insulin data at weeks 24 and 34 were isolated from the same windows as HbA1c values. If no value was available within the analysis window, the corresponding outcome was treated as missing.

Analysis of outcomes

Statistical analyses were performed on an intention-to-treat basis including all participants with at least 96 hours of sensor glucose data between 16 weeks' gestation and delivery. For each outcome, the groups were compared using a linear mixed effects regression model adjusting for baseline time in range, insulin delivery, and clinical site as a random effect. A per-protocol analysis was performed, using inverse probability of treatment weighting for whether a participant met the per-protocol analysis requirements (111). All p-values are two-tailed. Analyses were performed using SAS 9.4.

Subgroup analyses

The treatment effect for the primary outcome in the following subgroups was assessed: insulin delivery method at baseline, baseline HbA1c, maternal age, and clinical site.

Per-protocol analysis

A per-protocol analysis was performed, using inverse probability of treatment weighting for whether a participant met the per-protocol analysis requirements. A logistic regression model for a participant's fulfilment of per-protocol requirements was fitted with baseline time in range and age as the explanatory variables. Participant weights were used in the same linear mixed effects regression model described above, with participants included if they completed the 34-36 week visit or delivered prior to the 34-36 week visit, had a minimum of 96 hours of CGM data from 16 weeks' gestation to delivery, and had ≥60% hybrid closed-loop use if they were in the intervention group.

Multiple comparisons

For the primary outcome and key secondary outcomes, the Holm step-down method was used to control the Type 1 Error. Confidence intervals for the other secondary outcomes were not adjusted.

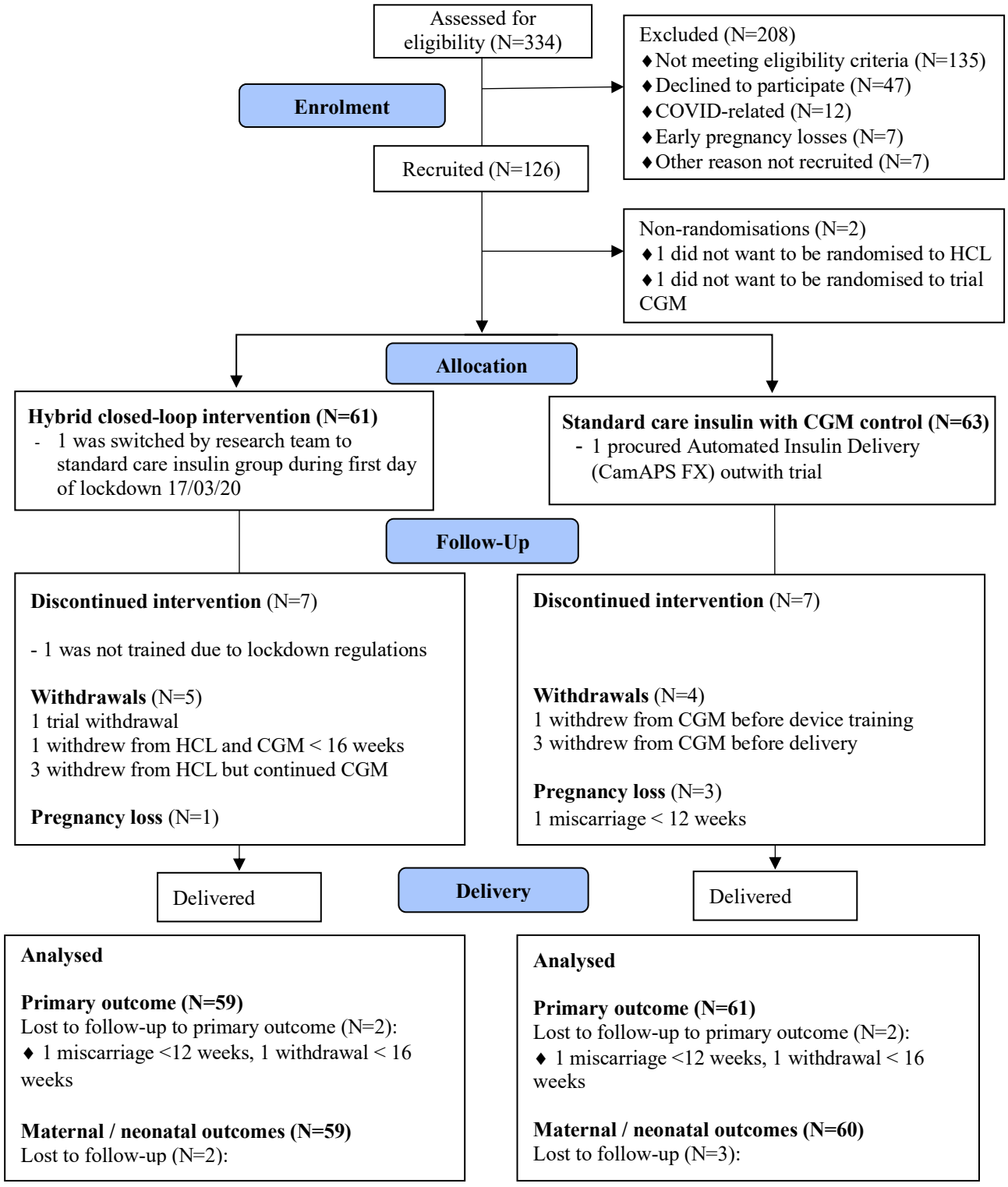
2.5 Results

Participants

Between September 2019 and March 2022, 334 participants were assessed for eligibility. Among 199 potentially eligible women 126 were enrolled and 124 were randomised. 61 participants were assigned to the hybrid closed-loop intervention group and 63 to the standard care control group (Figure 2.5). Participants were recruited from nine NHS maternity clinics, had a mean (± SD) age of 31.1 ± 5.3 years, and mean early pregnancy HbA1c of 61 ± 13mmol/mol. The recruited population was representative of the pregnant women with type 1 diabetes in the United Kingdom (Tables 2.2 – 2.4). Almost all participants (98%) were using continuous glucose monitoring (mostly intermittent e.g. Abbott FreeStyle Libre2 CGM) and approximately half (46%) were using insulin pump therapy at the time of enrolment. More participants in the hybrid closed-loop group were multiparous (66% vs. 40%), while those in standard care reported more previous diabetic ketoacidosis events (ten participants vs. one participant).

Two participants did not adhere to their assigned treatment; one intervention participant (lockdown restrictions prevented hybrid closed-loop training), and one standard care participant who procured automated insulin delivery (by self-funding the CamAPS FX) outside of the trial (Figure 2.5). Seven participants in each group discontinued their assigned treatment; the timing and reasons for which are listed in Table 2.5).

Figure 2.5 Consort diagram



Reasons for not meeting trial eligibility criteria (N=135) were: HbA1c out of range (N=60), unwilling to use study devices/switch from current treatment methods (N=32), outside of gestational age window (>13 weeks 6 days' gestation) (N=24), other reasons

Table 2.2 Baseline characteristics of AiDAPT trial participants

	Hybrid closed-loop (N = 61)	Standard care (N = 63)	Overall (N = 124)
Age (years)			
18-25	9 (15%)	15 (24%)	9 (15%)
26-35	41 (67%)	38 (60%)	41 (67%)
≥ 36	11 (18%)	10 (16%)	11 (18%)
Mean ± SD	32.0 ± 5.0	30.2 ± 5.5	31.1 ± 5.3
Range	19.9 to 42.7	19.7 to 44.7	19.7 to 44.7
Race / Ethnicity			
White	58 (95%)	57 (90%)	115 (93%)
Black	1 (2%)	3 (5%)	4 (3%)
Asian	1 (2%)	2 (3%)	3 (2%)
Other/More than one race	1 (2%)	1 (2%)	2 (2%)
Diabetes duration (years)			
1-<5	4 (7%)	5 (8%)	9 (7%)
5-<10	8 (13%)	9 (14%)	17 (14%)
≥ 10	49 (80%)	49 (78%)	98 (79%)
Mean ±SD	18 ± 8	16 ± 7	17 ± 8
Range	2 to 31	2 to 33	2 to 33
Maternal weight (kg)$^{\alpha}$			
Mean ±SD	76.0 ± 16.4	73.3 ± 14.0	74.7 ± 15.2
Range	49.0 to 138.0	53.9 to 117.8	49.0 to 138.0
Maternal BMI (kg/m^2)			
Mean ± SD	27.9 ± 5.9	26.9 ± 4.8	27.4 ± 5.3
Range	18.0 to 48.9	19.9 to 41.2	18.0 to 48.9
Higher education (University undergraduate / postgraduate degree or equivalent)	36 (59%)	33 (52%)	69 (56%)
Recruitment gestation (weeks)			
Median (quartiles)	10.3 (8.0-11.7)	10.0 (8.4-11.3)	10.0 (8.4, 11.6)
Range	6.7 to 13.7	6.1 to 14.3	6.1 to 14.3
Randomisation gestation (weeks)			
Median (quartiles)	11.3 (9.6-13.0)	11.0 (9.6-12.4)	11.1 (9.6, 12.7)
Range	7.7 to 15.0	7.7 to 16.3	7.7 to 16.3
Past Diabetes / Medical History			
Diabetes complications	35 (57%)	35 (56%)	70 (56%)
Retinopathy	35 (57%)	34 (54%)	69 (56%)
Nephropathy	4 (7%)	5 (8%)	9 (7%)
Neuropathy	4 (7%)	2 (3%)	6 (5%)
Prior diabetic ketoacidosis$^{\beta}$	1 (2%)	10 (16%)	11 (9%)
Prior severe hypoglycaemia$^{\delta}$	4 (7%)	5 (8%)	9 (7%)
Chronic hypertension	4 (7%)	2 (3%)	6 (5%)
Systolic BP	117.8 ± 11.9	117.3 ± 12.9	117.5 ± 12.3
Diastolic BP	69.4 ± 9.3	68.3 ± 9.4	68.8 ± 9.3

Pregnancy history			
Previous pregnancies >24 weeks' gestation			
0	21 (34%)	38 (60%)	59 (48%)
1	23 (38%)	21 (33%)	44 (35%)
2	14 (23%)	3 (5%)	17 (14%)
≥ 3	3 (5%)	1 (2%)	4 (4%)
Previous pregnancy loss$^{\phi}$	21 (34%)	20 (32%)	41 (32%)
Pre-pregnancy factors			
Folic acid	38 (62%)	34 (54%)	52 (42%)
Alcohol	36 (59%)	36 (57%)	72 (58%)
Smoking	10 (16%)	14 (22%)	24 (19%)
HbA1c during early pregnancy$^{\lambda}$			
≥ 42 - <53mmol/mol	23 (38%)	13 (21%)	36 (29%)
≥ 53 - <64mmol/mol	21 (34%)	24 (38%)	45 (36%)
≥ 64 mmol/mol	17 (28%)	26 (41%)	43 (35%)
Mean ± SD (mmol/mol)	59 ± 12	63 ± 14	61 ± 13
Range (mmol/mol)	42 to 103	48 to 130	42 to 130
Continuous glucose monitoring$^{\pi}$	59 (97%)	62 (98%)	121 (98%)
Abbott Freestyle Libre	43 (73%)	47 (76%)	90 (74%)
Dexcom CGM	12 (20%)	14 (23%)	26 (21%)
Medtronic CGM	4 (7%)	1 (2%)	5 (4%)
Insulin delivery			
Insulin pump	32 (52%)	25 (40%)	57 (46%)
Multiple daily injections	27 (44%)	37 (59%)	64 (52%)
Automated insulin delivery$^{\theta}$	2 (3%)	1 (2%)	3 (2%)
Total daily insulin (U/kg/day)			
Mean ±SD	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Range	0.3 to 1.3	0.3 to 1.4	0.3 to 1.4

Number (%) unless otherwise stated.

α Maternal weight at first medical appointment in pregnancy (booking appointment)

β Participants in standard care had more diabetic ketoacidosis (DKA) events in the 12 months before enrolment. 9 standard care participants reported 1 DKA event and 1 reported >10 DKA events.

δ Severe hypoglycaemia (SH) events defined as requiring third party assistance in the 12 months before enrolment. 4 standard care participants reported 1 SH event and 1 reported 3 SH events. 3 hybrid closed-loop participants reported 1 SH and 1 reported 2 SH events.

ϕ Includes previous miscarriages and pregnancy terminations. 15 participants in each group reported 1 pregnancy loss, 6 hybrid closed-loop and 5 standard care participants reported 2 or more pregnancy losses.

λ 1 participant with HbA1c 42mmol/mol was entered during the pandemic (Mar 2020) whilst experiencing frequent hypoglycaemia using an alternative closed-loop (Tandem Control IQ) system.

π Continuous glucose monitoring at the time of enrolment

θ Participants using alternative hybrid closed-loop systems were eligible. Two (1 DIY loop Android APS via Accuchek Insight, 1 Tandem Control IQ) were randomized to the intervention group and 1 to standard care (Medtronic 780G).

Table 2.3 Trial site recruitment

Sites	Hybrid closed-loop (N=61)	Standard care (N=63)
Cambridge University Hospitals NHS Foundation Trust	11	11
St Thomas' Hospital, London	6	7
Norfolk and Norwich University Hospital NHS Foundation Trust	19	21
King's College Hospital NHS Foundation Trust	6	6
NHS Greater Glasgow and Clyde	6	5
Royal Infirmary of Edinburgh	5	5
Belfast Health and Social Care Trust	2	1
Leeds Teaching Hospitals NHS Foundation Trust	1	1
East Suffolk and North Essex NHS Foundation Trust	5	6
Total	61	63

Table 2.4 Representativeness of AiDAPT trial participants (112)

Condition under investigation: Pregnancy complicated by Type 1 Diabetes (T1D)	
Special considerations related to:	
Sex and gender	Pregnant women
Age	Women of reproductive years aged 18-45years
Race or ethnic group	The T1D pregnant population are predominantly White, with 91% White ethnicity based on population-based data in the UK. (6)
Geography	Prevalence of T1D is higher in Northern Europe, with approximately 2,000 T1D pregnancies per year in the UK. The onset of T1D at a lower age is increasing so women are now entering pregnancy with longer duration of T1D.
Other considerations	Maternal age, parity (number of previous pregnancies), BMI and duration of T1D are important factors in relation to diabetes and pregnancy complications. Although women with T1D are advised to plan for pregnancy (take 5mg folic acid, and aim for HbA1c <48mmol/mol), approximately 50% of T1D pregnancies are unplanned. Most women (85%) do not achieve HbA1c <48mmol/mol. The mean HbA1c during early pregnancy, is 60mmol/mol at 7 weeks' gestation, at the first contact with specialist diabetes pregnancy teams. Complications in babies of mothers with T1D are common, with population-based data from the UK showing that 57% of babies are large for gestational age, 47% are delivered preterm <37 weeks' gestation, and 51% are admitted to neonatal care units. (113)
Overall representativeness of this trial	Our age range was from 19.7 to 44.7 (mean 31.1) years reflecting the pregnant population with T1D. Participants were predominantly White (92.7%), with smaller numbers self-identifying as Asian (3.9%), Black (2.1%) and Mixed/Other racial or ethnic groups (2.9%). The duration of T1D ranged from 2 to 33 (mean 17) years, meaning that our T1D duration was 4 years longer than the population average of 13 years. Our participants' BMI ranged from 18.0 to 48.9 kg/m^2 with 37% having a healthy BMI category, 37% overweight and 26% obese, reflecting high rates of maternal overweight and obesity. We included women across maternal glucose categories with entry HbA1c ranging from 6.0% to 14.0% (mean 7.7%). Our study population had longer duration of T1D, and higher rates of diabetes complications (57% vs 37% retinopathy). However, overall maternal age, ethnicity, pregnancy planning and baseline HbA1c characteristics are very similar to the national UK T1D pregnant population during 2019-2020.

Despite the impact of the COVID-19 pandemic, the proportion of completed study visits was high, ~95% from 16 weeks until delivery (Figure 2.6). Participants in the standard care group had more additional clinic visits (1.5 vs 1.1) and more unscheduled contacts (9.6 vs 6.1), mostly for pregnancy and diabetes-related reasons (Tables 2.6 – 2.7). The frequency of CGM sensor use was consistently high, median 97% across both treatment groups (Table 2.8, Figure 2.7). The frequency of hybrid closed-loop use was also high in the intervention hybrid closed-loop group (median 96%) and remained >95% throughout pregnancy (Table 2.7, Figure 2.8).

Table 2.5 Compliance with treatment protocol

Reason[α]	**Hybrid closed-loop (N=61 randomised)**	**Standard care (N=63 randomised)**
<96 hours CGM data from 16 weeks until delivery[β]	2	2
Participants who did not complete the 34-36 week visit[δ]	2	4
Intervention group: HCL active for <60% of the time[ϕ]	7	n/a
Included in Per Protocol analysis	54	59

HCL = hybrid closed-loop

α Participants may have several reasons for exclusion

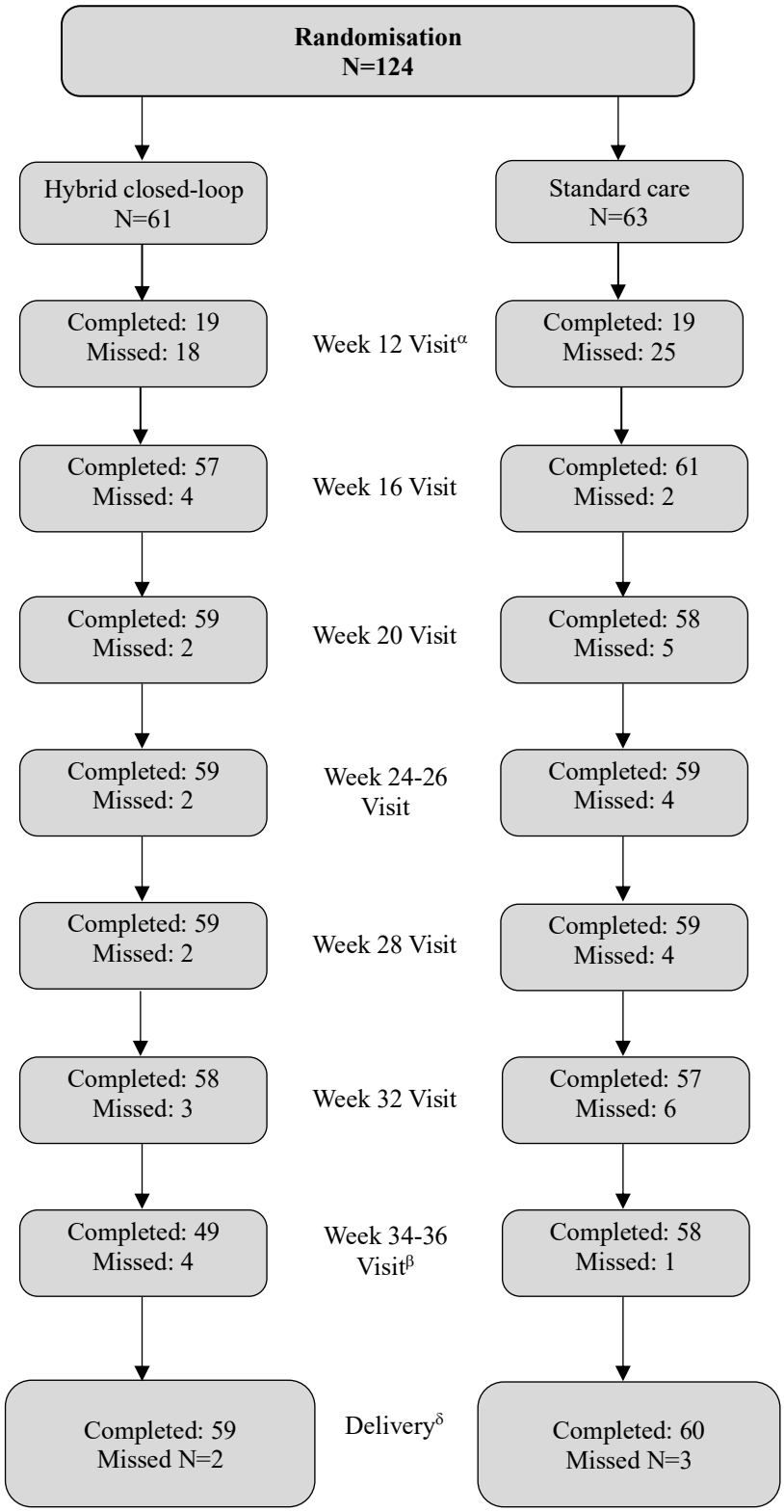
β Reasons for <96 hours' CGM data in intervention group were 1 miscarriage <12 weeks, 1 withdrawal of a previous HCL user 17 days post training. Reasons in standard care were 1 miscarriage <12 weeks, 1 withdrawal of previous Abbott Freestyle Libre user before CGM training.

δ Reasons for not completing the 34-36 weeks' visit (if not delivered by then) in the hybrid closed-loop group were 1 miscarriage <12 weeks, 1 withdrawal of a previous HCL user 17 days post training. Reasons in standard care were 1 miscarriage <12 weeks, 1 withdrawal of previous Abbott Freestyle Libre user before CGM training, 2 terminations of pregnancy (one for congenital anomaly). 3 standard care participants who completed the 34-36 weeks' visit but discontinued CGM in late pregnancy are included.

ϕ Reasons for HCL active <60% of the time in the intervention group were,

- 1 miscarriage <12 weeks' gestation.
- 1 intervention group participant was re-allocated to standard care by research team day 1 post randomisation due to the COVID-19 lockdown restrictions which prevented training.
- 4 withdrawals at days 15, 17, 17 and 21 post device training from participants who stated that HCL was not sufficiently aggressive/responsive. These included 1 previous HCL user (Tandem Control IQ) with entry HbA1c 42mmol/mol.
- 1 withdrawal with no hybrid closed-loop use from 16 weeks' gestation until delivery due to deteriorating medical co-morbidities (20 hyperemesis and severe ketosis events).

Figure 2.6 Completion of trial visits



α participants who were randomised before 12 weeks' gestation. Study visits were four-weekly so those randomized at 9-11 weeks' gestation did not require an additional 12 week visit.

β participants who had not delivered prior to the 34 -36 week visit

δ 5 participants (2 intervention, 3 control) did not have 96 hours of sensor data between 16 weeks and delivery. There were 5 out of window visits in the intervention group and 9 in the standard care group.

Table 2.6 Additional unscheduled visits and contacts by treatment group

	Hybrid closed-loop (N=61)	**Standard care (N=63)**
Number of unscheduled visits	**68**	**94**
Visits per participant Median (quartiles)	0 (0, 2)	0 (0, 2)
Visits per participant		
0	35 (57%)	34 (54%)
1	9 (15%)	13 (21%)
2	5 (8%)	4 (6%)
3	7 (11%)	4 (6%)
4	2 (3%)	3 (5%)
5	0 (0%)	1 (2%)
6	1 (2%)	1 (2%)
7	2 (3%)	1 (2%)
15	0 (0%)	1 (2%)
16	0 (0%)	1 (2%)
Number of unscheduled contacts[α]	**371**	**605**
Contacts per participant Median (quartiles)	2 (1, 4)	1 (0, 9)
Contacts per participant		
0	8 (13%)	24 (38%)
1-9	45 (74%)	24 (38%)
10-19	2 (3%)	3 (5%)
20-29	1 (2%)	3 (5%)
30-39	3 (5%)	4 (6%)
40-49	1 (2%)	2 (3%)
≥50	1 (2%)	3 (5%)

α Includes any telephone or video call, email or text messaging contact.

Table 2.7 Reasons for additional unscheduled visits and contacts

Reason for additional unscheduled visits	Hybrid closed-loop	Standard care
Additional CGM training	4	2
Additional insulin pump training	3	2
Additional closed-loop training	2	0
Additional protocol/procedure training or advice	0	0
Question or problem relating to diabetes management	15	25
Question or problem relating to pregnancy	35	51
Potential adverse event	2	3
Potential device deficiency	4	3
Needed study supplies	3	1
Other	14	21

*The same visit can have multiple reasons

Reason for additional unscheduled contacts[α]	Hybrid closed-loop	Standard care
Additional CGM training	19	35
Additional insulin pump training	29	8
Additional closed-loop training	61	1
Additional protocol/procedure training or advice	0	1
Question or problem relating to diabetes management	124	331
Question or problem relating to pregnancy	26	76
Potential adverse event	18	20
Potential device deficiency	29	29
Needed study supplies	43	48
Other	88	128

α Includes any telephone or video call, email or text messaging contact.
The same contact can have multiple reasons.

Table 2.8 CGM use by treatment group

A Frequency of CGM use in the hybrid closed-loop intervention group (N=61)

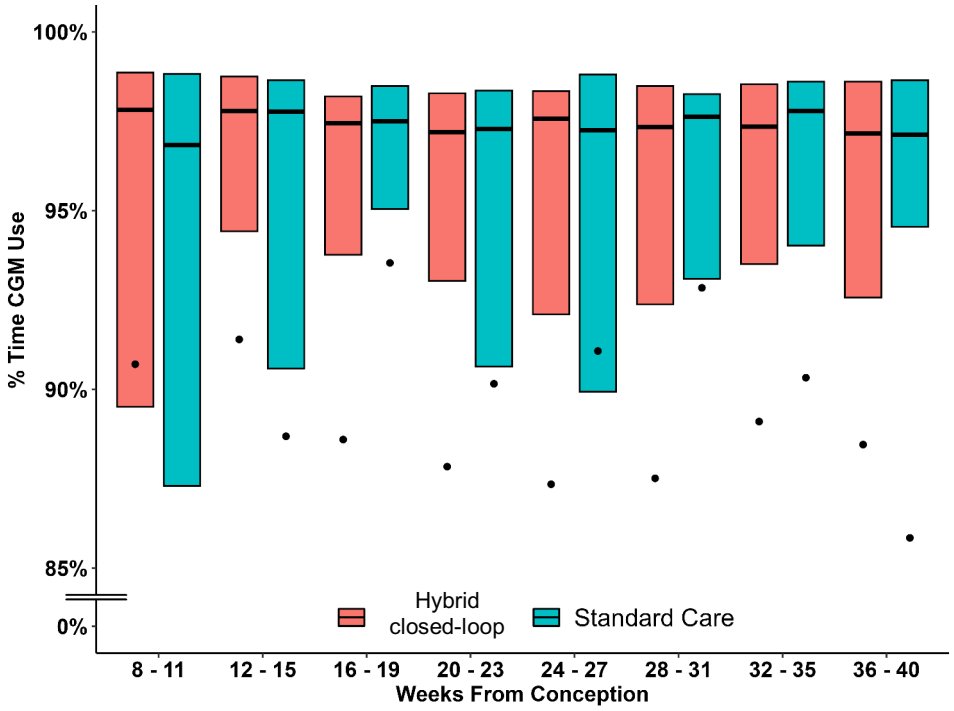
	24-hours	Daytime	Night time
% Time CGM use Median (quartiles)	97% (93%, 98%)	97% (92%, 98%)	98% (93%, 99%)
>90%	47 (77%)	47 (77%)	48 (79%)
80%-90%	2 (3%)	2 (3%)	2 (3%)
70%-80%	3 (5%)	3 (5%)	2 (3%)
60%-70%	2 (3%)	2 (3%)	2 (3%)
50%-60%	2 (3%)	2 (3%)	2 (3%)
<50%	3 (5%)	3 (5%)	3 (5%)
0%	2 (3%)	2 (3%)	2 (3%)

B Frequency of CGM use in the standard care control group (N=63)

	24-hours	Daytime	Night time
% Time CGM use Median (quartiles)	97% (91%, 98%)	96% (91%, 98%)	96% (90%, 99%)
>90%	47 (75%)	47 (75%)	44 (70%)
80%-90%	8 (13%)	8 (13%)	9 (14%)
70%-80%	3 (5%)	3 (5%)	2 (3%)
60%-70%	1 (2%)	1 (2%)	2 (3%)
50%-60%	1 (2%)	1 (2%)	1 (2%)
<50%	1 (2%)	1 (2%)	3 (5%)
0%	2 (3%)	2 (3%)	2 (3%)

Figure 2.7 CGM use by treatment group throughout pregnancy

This figure shows side by side boxplots of the continuous glucose monitoring (CGM) use for each treatment group, by 4-week antenatal period following device training.



Black bars denote medians and black dots denote means.

Table 2.9 Hybrid closed-loop system use in the intervention group

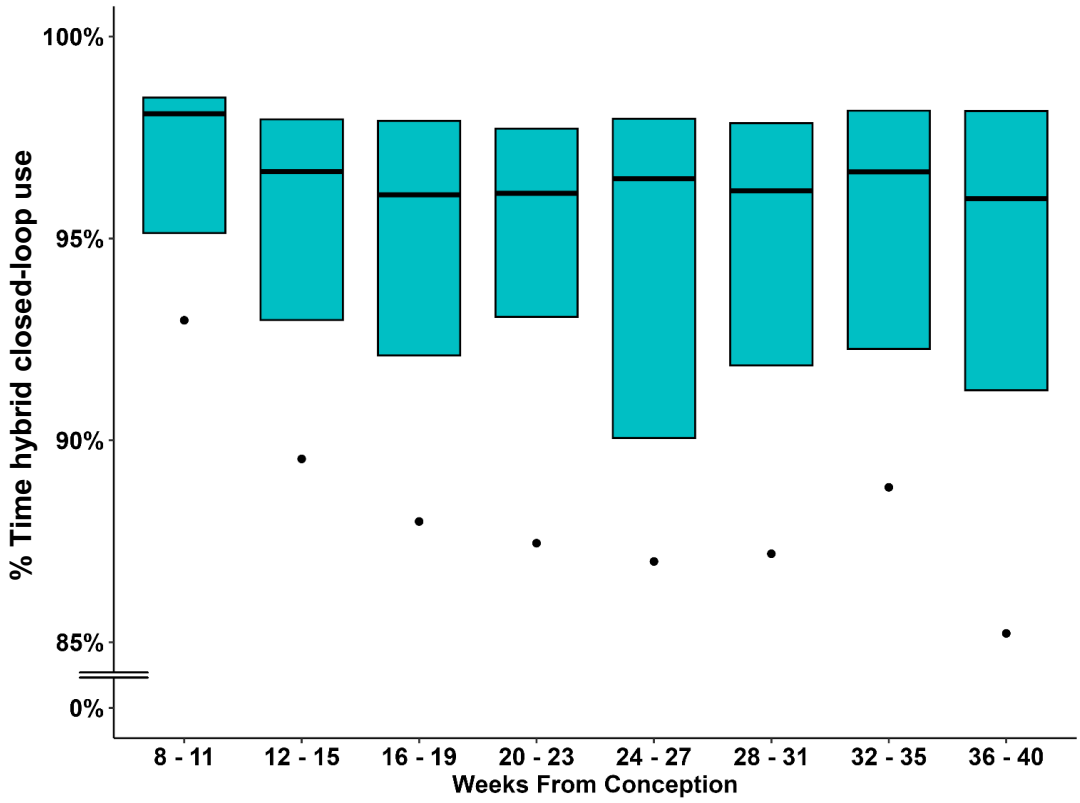
Frequency of CamAPS FX hybrid closed-loop system use in the intervention group (N=61)

	24-hours	Daytime	Nighttime
% Time HCL use Median (quartiles)	96% (94%, 98%)	96% (93%, 97%)	97% (95%, 99%)
>90%	49 (80%)	48 (79%)	52 (85%)
80%-90%	5 (8%)	5 (8%)	2 (3%)
70%-80%	0 (0%)	1 (2%)	0 (0%)
60%-70%	0 (0%)	0 (0%)	0 (0%)
50%-60%	0 (0%)	0 (0%)	0 (0%)
<50%	2 (3%)	2 (3%)	2 (3%)
0%	5 (8%)	5 (8%)	5 (8%)

Figure 2.8 Frequency of hybrid closed-loop use throughout pregnancy

This figure shows boxplots of the CamAPS FX hybrid closed-loop system use in the intervention group, by 4-week antenatal period following device training.

Black bars denote medians and black dots denote means.



Primary outcome

The mean (± SD) percentage of time that maternal glucose levels were within the pregnancy target range (3.5-7.8mmol/L) differed between study arms. Hybrid closed-loop users time in range increased from 47.8 ± 16.4% at baseline to 68.2 ± 10.5% during pregnancy (16 weeks' gestation until delivery) whereas standard care group participants went from 44.5 ± 14.4% to 55.6 ± 12.5%. The mean adjusted difference between the two groups was 10.5% (95% CI 7.0% to 14%; $p < 0.001$) (Figure 2.9, Table 2.10).

There were no variations in the treatment effect among trial sites and no differential effects across maternal age, HbA1c or insulin delivery categories (Figure 2.10). The large treatment difference was consistent between intention to treat and per protocol analysis (Table 2.11).

Figure 2.9 Percentage time spent in the pregnancy target glucose range
This figure shows the cumulative distribution of the percentage of time that the glucose level was within the pregnancy-specific target glucose range of 3.5-7.8 mmol/L, as measured by continuous glucose monitoring, for each treatment group from 16 weeks' gestation to delivery.

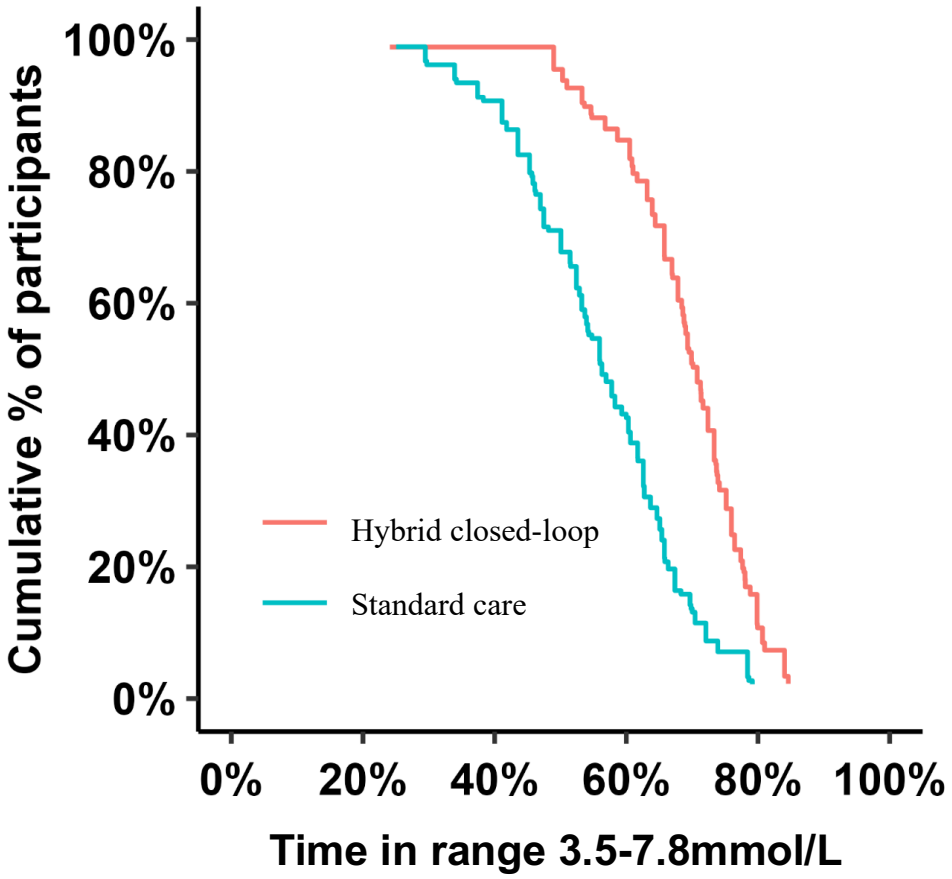


Table 2.10 Primary and secondary maternal glucose outcomes

Outcomes	Baseline[α]		Antenatal Intervention Phase[β]		Adjusted Treatment Difference[δ] (95% CI)
	Hybrid closed-loop (N=59)	Standard care (N=59)	Hybrid closed-loop (N=59)	Standard care (N=61)	
Hours of sensor data	150 (128, 156)	149 (124, 171)	3361 (2996, 3561)	3417 (3112, 3507)	n/a
Primary Outcome					
% Time in range 3.5-7.8mmol/L	**47.8% ± 16.4%**	**44.5% ± 14.4%**	**68.2% ± 10.5%**	**55.6% ± 12.5%**	**10.5% (7.0%, 14.0%)[ϕ]**
Key Secondary Outcomes					
%Time >7.8mmol/L	**48.7% ± 18.0%**	**51.8% ± 16.2%**	**29.2% ± 10.6%**	**41.4% ± 13.2%**	**-10.2% (-13.8%, -6.6%)**
%Overnight time in range[α] 3.5-7.8mmol/L	**47.4% ± 20.8%**	**44.5% ± 16.6%**	**70.8% ± 11.2%**	**56.7% ± 13.6%**	**12.3% (8.3%, 16.2%)**
Secondary outcomes					
%Time 3.5-10.0mmol/L	71% ± 16%	68% ± 15%	87% ± 9%	80% ± 10%	6% (3%, 9%)
%Time >10.0mmol/L	26% ± 17%	28% ± 16%	11% ± 9%	17% ± 11%	-6% (-9%, -3%)
Mean glucose (mmol/L)[γ]	8.3 ± 1.6	8.4 ± 1.3	7.0 ± 0.8	7.6 ± 0.9	-0.5 (-0.8, -0.3)
HbA1c (mmol/mol)	59 ± 12	63 ± 14	42 ± 5	47 ± 6	-3.4 (-5.5, -1.3)
Glucose SD (mmol/L)[λ]	3.0 ± 0.8	3.1 ± 0.7	2.3 ± 0.6	2.6 ± 0.6	-0.2 (-0.4, -0.1)
Glucose CV (%)[λ]	36% ± 5%	37% ± 6%	33% ± 5%	34% ± 5%	-1.1% (-2.6%, 0.3%)
Hypoglycaemia					
%Time <3.5mmol/L	2.75% (0.86%, 4.87%)	2.22% (0.72%, 6.00%)	2.26% (1.54%, 3.31%)	2.02% (1.25%, 4.37%)	-0.4% (-1%, 0.2%)
%Time <3.0mmol/L	1.05% (0.07%, 2.37%)	0.79% (0.18%, 2.28%)	0.71% (0.49%, 1.19%)	0.73% (0.36%, 1.67%)	-0.2% (-0.45%, 0.1%)
Mild hypoglycaemia events[π]	6.4 (2.2, 11.5)	5.5 (2.4, 11.1)	6.7 (4.6, 9.4)	5.7 (3.1, 9.4)	0.2 (-1.1, 1.4)
Moderate hypoglycaemia events[π]	2.2 (0.0, 5.7)	2.2 (0.0, 5.9)	2.3 (1.6, 3.8)	2.1 (1.1, 4.4)	0.0 (-0.47, 0.7)
Overnight Outcomes (23.00-07.00 hours)					
Mean glucose (mmol/l)	8.3 ± 1.8	8.4 ± 1.4	6.9 ± 0.8	7.5 ± 1.0	-0.5 (-0.8, -0.2)
%Time >7.8mmol/L	49% ± 22%	52% ± 18%	27% ± 11%	40% ± 14%	-12% (-16%, -8%)
%Time <3.5mmol/L	1.40% (0.00%, 5.27%)	2.33% (0.51%, 5.67%)	1.56% (1.10%, 2.51%)	2.57% (1.04%, 4.41%)	-1.4% (-2.1%, -0.46%)
Glucose SD (mmol/l)	2.9 ± 0.9	3.0 ± 0.8	2.2 ± 0.6	2.6 ± 0.6	-0.3 (-0.5, -0.1)
Glucose CV (%)	35% ± 8%	36% ± 8%	32% ± 5%	35% ± 6%	-2.5% (-4.4%, -0.6%)

Mild hypoglycaemia events[π]	3.5 (0.0, 10.2)	6.4 (0.0, 11.9)	4.3 (2.9, 5.5)	5.3 (2.8, 8.7)	-1.8 (-3.1, -0.5)
Moderate hypoglycaemia events[π]	0.0 (0.0, 4.7)	0.0 (0.0, 6.9)	1.7 (1.0, 2.5)	2.1 (0.8, 4.3)	-0.7 (-1.4, -0.0)

Plus–minus values are means ±SD. Otherwise data are median (quartiles).

α Baseline values were calculated with the use of data assessed by continuous glucose monitoring during the pre-randomisation run-in phase. Two participants were missing baseline data assessed by continuous glucose monitoring. Four participants whose follow-up data assessed by continuous glucose monitoring were missing because of a miscarriage or termination of pregnancy are not included here.

β Antenatal intervention phase is from 16 weeks' gestation until delivery. Outcomes were calculated with the use of sensor data assessed by continuous glucose monitoring except for the HbA1c level, which was measured at the trial sites. Four participants were missing intervention data assessed by continuous glucose monitoring. The HbA1c level at 34 to 36 weeks' gestation reflects maternal levels over the preceding 10 to 12 weeks.

δ The model was adjusted for baseline value, baseline insulin delivery method, and clinical site as a random effect. Differences in outcomes that were measured as percentages are given in percentage points. $P < 0.001$ for the between-group comparison of the primary outcome.

ϕ Difference is hybrid closed-loop – standard care. Results were similar when adjustment was made for the number of previous diabetic ketoacidosis events, when previous pregnancies were considered as covariates, and when site was treated as a fixed effect (mean difference, 10.6 percentage points; 95% CI, 7.0 to 14.1).

γ Shown are the means of the individual participants' mean glucose levels.

λ The glucose SD and coefficient of variation (CV) values indicate within-participant variability of continuous glucose monitor measurements.

π Mild hypoglycaemia was defined as a glucose level of <3.5mmol/L as assessed by continuous glucose monitoring for at least 15 consecutive minutes, with episodes separated by 30 minutes or more. Moderate hypoglycaemia was defined as a glucose level of <3.0mmol/L as assessed by continuous glucose monitoring for at least 15 consecutive minutes, with episodes separated by 30 minutes or more.

Figure 2.10 Subgroup analyses for primary outcome (% time in range 3.5-7.8mmol/L)

HCL = hybrid closed-loop, MDI = multiple daily injections, AID = automated insulin delivery

	Hybrid closed-loop		Standard care		
Group	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**Adjusted Treatment Difference (95% CI)**
Overall	59	68.2% ± 10.5%	61	55.6% ± 12.5%	10.5% (6.2%, 14.8%)
SiteID					
A	19	66.9% ± 13.2%	21	56.8% ± 11.1%	6.6% (0.4%, 12.9%)
B	10	68.9% ± 11.7%	10	53.9% ± 11.9%	10.3% (1.2%, 19.3%)
C	6	67.8% ± 7.0%	6	57.4% ± 14.5%	14.7% (3.3%, 26.0%)
D	6	66.2% ± 7.2%	5	59.6% ± 6.0%	9.7% (-2.3%, 21.6%)
E	5	73.1% ± 11.5%	6	60.5% ± 16.8%	12.6% (0.9%, 24.3%)
F	5	64.4% ± 9.7%	5	42.8% ± 17.1%	18.5% (6.3%, 30.7%)
G	5	69.5% ± 5.0%	6	56.3% ± 11.9%	12.7% (0.8%, 24.5%)
H	2	73.6% ± 7.4%	1	58.3%	21.8% (-5.9%, 49.6%)
I	1	77.8%	1	45.8%	24.7% (-2.7%, 52.0%)
Age					
18 - <26 years	9	70.1% ± 7.0%	15	50.6% ± 13.0%	13.2% (4.9%, 21.5%)
26 - <36 years	41	68.1% ± 11.3%	37	56.8% ± 12.4%	10.3% (5.9%, 14.7%)
≥ 36 years	9	66.9% ± 9.9%	9	59.0% ± 11.3%	11.5% (2.1%, 20.9%)
Baseline HbA1c (mmol/mol)					
<53	22	72.2% ± 7.7%	12	63.6% ± 9.9%	7.5% (0.9%, 14.1%)
53 - <64	20	68.8% ± 9.7%	23	59.5% ± 8.8%	10.9% (5.4%, 16.4%)
≥64	17	62.3% ± 12.2%	26	48.5% ± 13.0%	11.9% (6.3%, 17.6%)
Insulin Modality at Baseline					
Pump	30	70.1% ± 8.6%	24	57.7% ± 10.3%	11.8% (6.5%, 17.1%)
MDI	27	65.2% ± 11.7%	36	54.2% ± 13.9%	10.2% (5.3%, 15.0%)
AID	2	80.0% ± 5.7%	1	58.3%	17.2% (-6.0%, 40.5%)

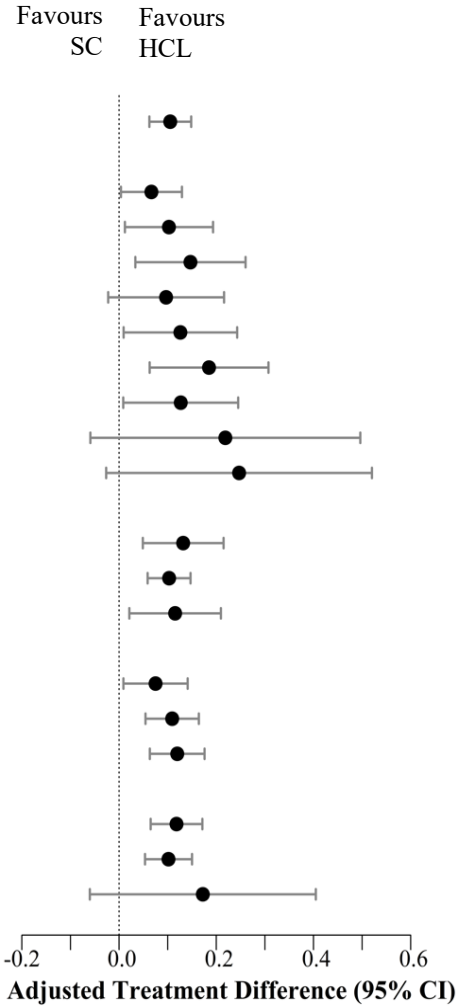


Table 2.11 Per-protocol analysis

Outcomes	Baseline		Intervention Phase[α]		P-value[β]
	Hybrid closed-loop (N=54)	**Standard care (N=57)**	**Hybrid closed-loop (N=54)**	**Standard care (N=59)**	
Hours of sensor data	151 (128, 162)	149 (124, 168)	3,381 (3,087, 3,562)	3,421 (3,169, 3,510)	
% Time in range 3.5-7.8mmol/L	48.7% ± 16.4%	45.4% ± 13.9%	69.5% ± 8.5%	56.4% ± 12.0%	n/a
Change from baseline	n/a	n/a	20.8% ± 14.2%	10.9% ± 11.8%	n/a
Adjusted Treatment Difference[β,δ] *mean (95% CI)*	n/a		12.1% (8.6%, 15.6%)		<0.001

Plus–minus values are means ±SD. Otherwise data are medians (quartiles).

α CGM data calculated from 16 weeks' gestation until delivery

β Model adjusted for baseline %time spent between 3.5-7.8mmol/L, baseline insulin delivery method, and clinical site as a random effect. Model used inverse probability of treatment weighting.

δ Difference is hybrid closed-loop – standard care. Excludes seven participants from the hybrid closed-loop group and 4 participants from the standard care group. The timings and reasons for per-protocol analysis exclusions are outlined in Table 2.5.

Secondary glycaemic outcomes

Participants randomised to hybrid closed-loop spent less time with glucose levels above target range (>7.8mmol/mol): mean difference -10.3% (95% CI -13.8% to -6.6%) (Table 2.10). The effects of the intervention during the overnight period (23.00-07.00) closely followed the overall 24-hour results: mean difference 12.3% (95% CI 8.3% to 16.2%). This was accompanied by improved glycaemic control in the hybrid closed-loop group including lower mean glucose (mean difference -0.5mmol/L [95% CI -0.8 to -0.3mmol/L]); lower HbA1c (mean difference -3.4mmol/mol [95%CI -5.5 to -1.3mmol/mol]) and fewer nocturnal hypoglycaemic events. In the hybrid closed-loop group there were 4.3 mild hypoglycaemia episodes and 1.7 moderate hypoglycaemia episodes compared to 5.3 mild episodes and 2.1 moderate episodes in the standard care group. This is especially notable since participants in both groups spent ~70% time in the near-optimal (3.5-10.0mmol/L) target range at baseline. The median gestation at which participants were randomised was 11 weeks and those who were trained and started hybrid closed-loop therapy during the first trimester spent 5% more time in range between 3.5-7.8mmol/L by the end of 12 weeks' gestation (Table 2.12, Figure 2.11).

Attainment of the International Consensus on Time in Range CGM sensor glucose target of >70% time (16 hours 48 mins a day) within the pregnancy-specific range (3.5-7.8mmol/L) was achieved by 28 (47%) hybrid closed-loop participants and 7 (11%) standard care participants (Table 2.13). Maternal glucose improvements were achieved by lowering the CamAPS FX algorithm setting of the personal glucose targets (from 5.7 ± 0.1mmol/L to 5.1 ± 0.3mmol/L) across gestation and without additional hypoglycaemia, maternal weight gain or total daily insulin dose (Tables 2.10, 2.14 – 2.16).

Table 2.12 Secondary maternal glucose outcomes by trimester

Outcomes	Baseline		First Trimester		Second Trimester		Third Trimester	
	Hybrid closed-loop (N=61)	**Standard care (N=61)**	**Hybrid closed-loop (N=40)**	**Standard care (N=44)**	**Hybrid closed-loop (N=60)**	**Standard care (N=61)**	**Hybrid closed-loop (N=57)**	**Standard care (N=58)**
Hours of sensor data (Median, quartiles)	150 (128, 156)	149 (124, 168)	371 (219, 519)	378 (214, 567)	2,380 (2,066, 2,463)	2,418 (2,151, 2,462)	1,442 (1,181, 1,597)	1,494 (1,356, 1,572)
% Time 3.5-7.8mmol/L	47.7% ± 16.2%	44.8% ± 14.6%	59.2% ± 14.8%	53.3% ± 12.9%	65.8% ± 10.3%	52.6% ± 12.5%	71.2% ± 8.7%	59.7% ± 12.8%
Adjusted treatment difference *mean (95% CI)*			5.4% (0.9%, 9.9%)		11.9% (8.6%, 15.1%)		10.6% (7.1%, 14.2%)	
Mean glucose (mmol/L)	8.3 ± 1.6	8.4 ± 1.3	7.5 ± 1.1	7.7 ± 1.0	7.1 ± 0.8	7.8 ± 1.0	6.7 ± 0.5	7.3 ± 0.8
Adjusted treatment difference *mean (95% CI)*			-0.3 (-0.6, 0.1)		-0.6 (-0.8, -0.3)		-0.5 (-0.8, -0.3)	
% Time >7.8mmol/L	48.9% ± 17.8%	51.5% ± 16.3%	38.0% ± 15.5%	43.5% ± 13.9%	31.6% ± 10.6%	44.2% ± 13.4%	26.2% ± 9.0%	37.5% ± 13.3%
Adjusted treatment difference *mean (95% CI)*			-4.7% (-9.5%, 0.1%)		-11.1% (-14.6%, -7.6%)		-10.4% (-14.2%, -6.6%)	
% Time <3.5mmol/L	2.5% (0.8%, 4.8%)	2.2% (0.7%, 5.1%)	2.2% (1.1%, 4.0%)	2.1% (1.2%, 3.6%)	2.2% (1.6%, 3.6%)	2.1% (1.3%, 4.8%)	2.2% (1.4%, 3.3%)	2.7% (1.2%, 3.9%)
Adjusted treatment difference *mean (95% CI)*			-0.3% (-1.4%, 0.7%)		-0.6% (-1.2%, 0.1%)		-0.2% (-0.8%, 0.4%)	
Glucose SD (mmol/L)	3.0 ± 0.8	3.0 ± 0.7	2.7 ± 0.6	2.8 ± 0.6	2.5 ± 0.6	2.7 ± 0.6	2.1 ± 0.4	2.4 ± 0.5
Adjusted treatment difference *mean (95% CI)*			-0.1 (-0.3, 0.1)		-0.3 (-0.4, -0.1)		-0.2 (-0.4, -0.1)	
Glucose CV (%)	36% ± 5%	37% ± 6%	35% ± 5%	36% ± 6%	34% ± 5%	35% ± 5%	31% ± 4%	33% ± 5%
Adjusted treatment difference *mean (95% CI)*			-0.3% (-2.2%, 1.6%)		-0.9% (-2.3%, 0.5%)		-1.1% (-2.6%, 0.4%)	

Data are Mean ± SD unless otherwise stated
Difference is Hybrid closed-loop – Standard care adjusted for baseline value, baseline insulin delivery method, and clinical site as a random effect.

Figure 2.11 Percentage time spent in the pregnancy target glucose range

Figure A shows side by side boxplots of the percentage of time that the glucose level was within the pregnancy-specific target glucose range of 3.5-7.8mmol/L, as measured by continuous glucose monitoring, for each treatment group, over each 4-weekly antenatal time period from device training until delivery. The mean personal glucose target used by hybrid closed-loop participants during the first, second and third trimesters were 5.7mmol/L, 5.4mmol/L, and 5.1 mmol/L (Table 2.14).

Black bars denote medians and black dots denote means.

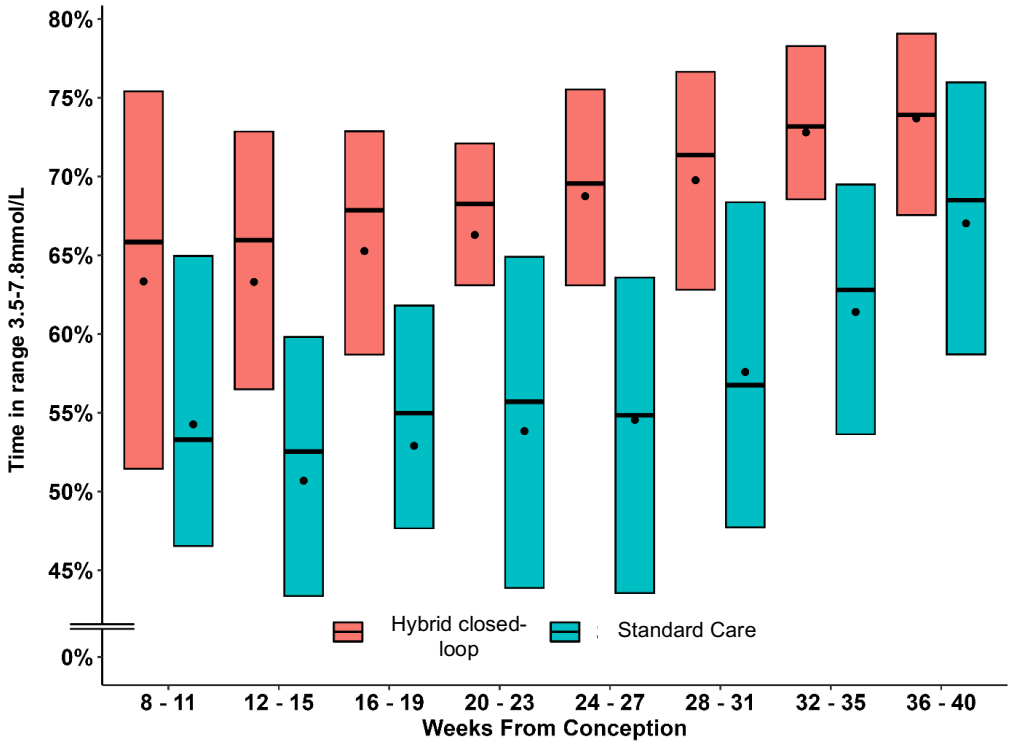


Figure B shows an envelope plot of the same pregnancy-specific target glucose range outcome, as measured by continuous glucose monitoring, for each treatment group, according to the time of day, from 16 weeks' gestation to delivery.

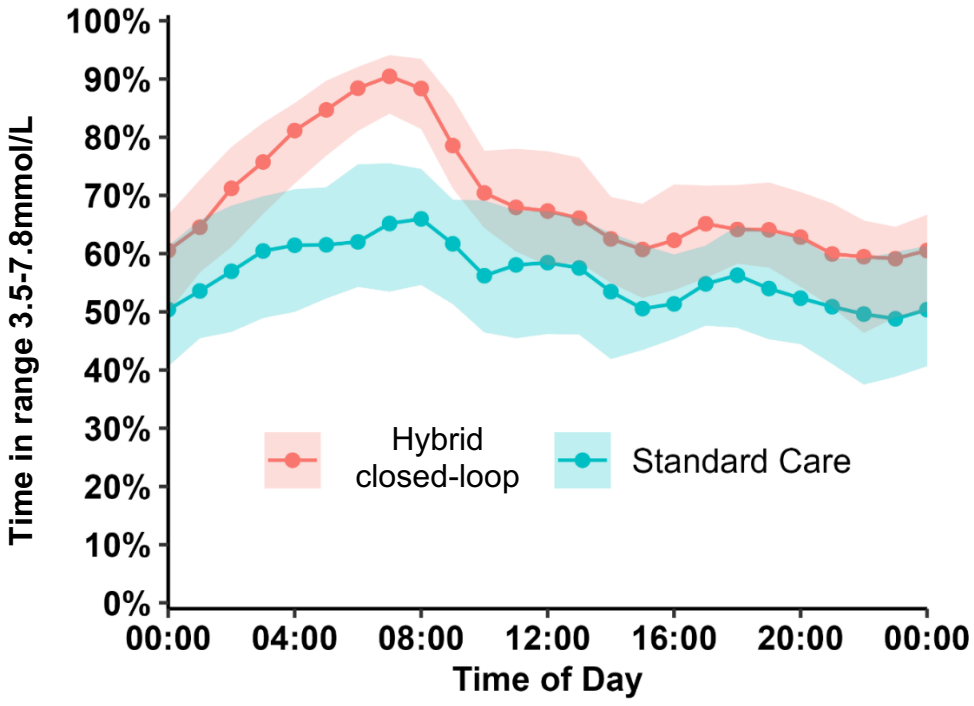


Table 2.13 Attainment of type 1 diabetes pregnancy glucose targets

The NICE HbA1c target is ≤ 48mmol/mol
The type 1 diabetes International Consensus on Time in Range pregnancy sensor glucose targets are:

- Time in range 3.5-7.8mmol/L for >70% (16hr 48min a day)
- Time above range >7.8mmol/L for <25% (6hr a day)
- Time below range <3.5mmol/L for <4% (1hr a day)
- Time <3.0mmol/L <1% (15min a day)

Outcomes	Baseline		Antenatal Intervention Phase[α]	
	Hybrid closed-loop (N=59)	Standard care (N=59)	Hybrid closed-loop (N=59)	Standard care (N=61)
Hours of sensor data Median (quartiles)	150 (128, 156)	149 (124, 171)	3,361 (2,996, 3,561)	3,417 (3,112, 3,507)
HbA1c ≤ 48mmol/mol			48 (83%)	36 (59%)
Achieving > 70% of time in range 3.5-7.8mmol/L			28 (47%)	7 (11%)
Achieving < 25% of time >7.8mmol/L			22 (37%)	7 (11%)
Achieving < 4% of time < 3.5mmol/L			47 (80%)	44 (72%)
Achieving < 1% of time <3mmol/L			38 (64%)	37 (61%)

Data are N (%) unless otherwise stated
α CGM data calculated from 16 weeks' gestation until delivery.

Table 2.14 Personal glucose target in the hybrid closed-loop group

Trimester[α]	N[β]	Mean Target *(mmol/L)*
1	34	5.7 ± 0.1
2	58	5.4 ± 0.3
3	53	5.1 ± 0.3

Data are Mean ± SD

α The first trimester is from the day after randomisation until 12 weeks 6 days' gestation, the second trimester is from 13 weeks until 27 weeks 6 days, and the third trimester is from 28 weeks until delivery.

β 27 participants without 1st trimester data, 3 participants without 2nd trimester data, 8 participants without 3rd trimester data

Table 2.15 Maternal insulin outcomes

	Baseline		Week 24-26		Week 34-36		Adjusted Treatment Difference* (95% CI)
	Hybrid closed-loop	**Standard care**	**Hybrid closed-loop**	**Standard care**	**Hybrid closed-loop**	**Standard care**	
Total daily insulin (Units/kg/day) N	61	60	58	54	56	56	
Mean ± SD	0.69 ± 0.23	0.69 ± 0.23	0.79 ± 0.30	0.81 ± 0.31	0.97 ± 0.43	1.06 ± 0.47	-0.10 (-0.25, 0.06)
% change from baseline (N)	NA	NA	58	52	56	55	
Mean ± SD	NA	NA	18% ± 35%	21% ± 42%	44% ± 52%	61% ± 69%	
Daily basal insulin (Units/kg/day) N	61	61	59	59	57	56	
Mean ± SD	0.37 ± 0.16	0.37 ± 0.15	0.40 ± 0.15	0.37 ± 0.18	0.47 ± 0.21	0.43 ± 0.23	0.04 (-0.03, 0.12)
% change from baseline (N)	NA	NA	59	58	57	56	
Mean ± SD	NA	NA	18% ± 48%	5% ± 42%	36% ± 61%	21% ± 60%	
Daily Bolus Insulin (Units/kg/day) N	61	61	58	54	56	56	
Median (quartiles)	0.31 (0.23, 0.37)	0.30 (0.22, 0.40)	0.32 (0.23, 0.51)	0.41 (0.30, 0.50)	0.42 (0.28, 0.65)	0.55 (0.40, 0.84)	-0.13 (-0.26, 0.01)
% change from baseline N	NA	NA	58	52	56	55	
Median (quartiles)	NA	NA	9% (-11%, 50%)	42% (2%, 92%)	44% (-2%, 100%)	91% (35%, 208%)	

* Difference is hybrid closed-loop – standard care adjusted for baseline value, baseline insulin delivery method and clinical site as a random effect.

Maternal and neonatal outcomes

Out of the 63 participants assigned to standard care, there were three pregnancy losses: 1 first trimester miscarriage and two terminations of pregnancy. In the hybrid closed-loop group, there was one withdrawal <16 weeks' gestation and one first trimester miscarriage (Figure 2.5 and Table 2.16). There were five serious birth injuries across both groups: one shoulder dystocia occurred in the hybrid closed-loop group resulting in a fractured left clavicle. There were four babies born with hypoxic ischaemic encephalopathy in the standard care group, one as a result of shoulder dystocia with subsequent fractured left humerus and left Erb's palsy and one followed the onset of early preterm labour at 31 weeks' gestation, subsequent complicated emergency caesarean section and resulted in a neonatal death. Additional details on birth injuries are in Table 2.17.

We observed less gestational hypertension (new onset hypertension: 10% hybrid closed-loop vs. 32% standard care and pre-eclampsia: 7% hybrid closed-loop vs. 20% standard care) and more repeat elective caesarean sections in the hybrid closed-loop intervention group, likely related to there being more multiparous women in this arm. There were fewer large for gestational age babies born to mothers in the hybrid closed-loop group: 39% vs. 50% >90th centile on customised GROW (gestation-related optimal weight) chart. There were also fewer macrosomic babies (birthweight >4kg): 7% vs. 15%. Babies of mothers in the hybrid closed-loop group were delivered a mean of 4.5 days earlier (36+3 vs. 37+1 weeks' gestation), though without differences in preterm births, birthweight, neonatal complications, or rates of neonatal care admissions.

Table 2.16 Maternal and neonatal outcomes

	Hybrid closed-loop (N=59)	Standard care (N=60)
Maternal		
Hypertensive disorders (any)	12 (20%)	25 (42%)
Worsening of existing hypertension	4 (7%)	2 (3%)
New onset hypertension	6 (10%)	19 (32%)
Pre-eclampsia	4 (7%)	12 (20%)
Mode of delivery$^{\alpha}$		
Vaginal	10 (17%)	15 (25%)
Primary caesarean section	24 (41%)	34 (57%)
Repeat caesarean section	25 (42%)	11 (18%)
Caesarean type		
Planned / elective	27 (55%)	22 (49%)
Unplanned / emergency	22 (45%)	23 (51%)
Maternal weight gain (kg) [Mean ± SD]	11.1 ± 6.1	14.1 ± 6.1
Length of stay (days) [Median (quartiles)]	6 (4, 9)	6 (4, 8)
Fetal and Neonatal	**(N=60)**	**(N=63)**
Pregnancy loss <20 weeks$^{\beta}$	1	3
Neonatal death$^{\delta}$	0	1
Baby alive at discharge	59 (100%)	59 (98%)
Gestational age at delivery	$36^{+3} \pm 2$	$37^{+1} \pm 1$
Preterm births <37 weeks	27 (46%)	14 (23%)
Birthweight	**(N=59)**	**(N=60)**
Weight (kg) [Mean ± SD]	3.3 ± 0.6	3.5 ± 0.5
Median customised centiles (quartiles)$^{\phi}$	80.7 (53-97)	90.1 (71-99)
Small for gestational age	3 (5.1%)	1 (1.7%)
Large for gestational age	23 (39%)	30 (50%)
Extremely large for gestational age	13 (22%)	19 (31.7%)
Macrosomia >4.0kg	4 (7%)	9 (15%)
Neonatal Complications	**(N=59)**	**(N=60)**
Serious birth injury$^{\lambda}$	1 (2%)	4 (7%)
Respiratory distress	5 (8%)	8 (13%)
Hypoglycaemia Treated with IV or oral glucose	26 (44%)	25 (42%)
Hyperbilirubinaemia	40 (68%)	37 (62%)
Readmission within 7 days	8 (14%)	3 (5%)
NICU stay ≥1 day	13 (22%)	15 (25%)
Length of stay (days) Median (quartiles)	6 (3, 10)	5 (3, 7)

α Mothers in the hybrid closed-loop group had more previous births which likely contributed to more repeat (scheduled prior to the onset of labour) caesarean deliveries.

β 1 first trimester miscarriage in each group and 2 pregnancy terminations in standard care.

δ Neonatal death occurred approximately 12 hours after birth following onset of early preterm labour and severe hypoxic ischemic encephalopathy at 31 weeks' gestation.

ϕ Birthweight calculated using gestation-related optimal weight (GROW, version 8.0.6.2) centiles that adjust for neonatal sex, gestation, maternal height, weight, parity, and ethnicity. Small for gestational age is <10th centile, large for gestational age >90th centile and extremely large for gestational age >97.7th centile.

λ Birth injuries: see table 2.17 for further details

Table 2.17 Birth injuries, additional details

Treatment group	Description
Hybrid closed-loop	38+ weeks, induction of labour, operative vaginal delivery, birthweight 100th centile (>4kg) Shoulder dystocia - fractured left clavicle.
Standard care	37+ weeks, induction of labour, vaginal delivery, birthweight 99.7th centile (>4kg) Shoulder dystocia - fractured left humerus with left Erb's palsy & hypoxic ischaemic encephalopathy
Standard care	37+ weeks, emergency primary caesarean section, birthweight 80.5th centile (<4kg) Hypoxic ischaemic encephalopathy and left Erb's palsy
Standard care	37+ weeks, induction of labour, emergency primary caesarean section, birthweight 99.5th centile (<4kg) Hypoxic ischaemic encephalopathy
Standard care	31+ weeks, spontaneous preterm labour, complicated emergency repeat caesarean section, birthweight 56.4th centile (<4kg) Hypoxic ischaemic encephalopathy and neonatal death

Birthweight calculated using gestation-related optimal weight (GROW, version 8.0.6.2) centiles that adjust for neonatal sex, gestation, maternal height, weight, parity, and ethnicity.

Safety outcomes

There were six events of severe hypoglycaemia in the hybrid closed-loop group, and five in standard care (Table 2.18). There was also one episode of diabetic ketoacidosis in each group. One participant with severe hyperemesis experienced 20 non-acidotic ketosis events. Although assigned to the intervention arm, she did not use hybrid closed-loop between 16 weeks' gestation and delivery but contributed to the majority of ketosis and serious adverse events in the hybrid closed-loop group. The rate of adverse device events for the hybrid closed-loop system was 24.3 per 100 person years, with seven events related to hybrid closed-loop use and seven to the continuous glucose sensor (Table 2.19). One severe hypoglycaemia event related to the hybrid closed-loop was due to "user error", the participant forgot to update her insulin pump settings (relaxing the insulin to carbohydrate ratio) following a miscarriage and gave herself an incorrect bolus dose. A further episode of moderate ketosis occurred following loss of Bluetooth connectivity between the pump and CamAPS FX application (leading to discontinuation of hybrid closed-loop Auto Mode). Auto Mode reconnected automatically when the participant woke and ketosis and hyperglycaemia were resolving by the time the participant presented to maternity services with spontaneous preterm labour. A third adverse device event related to the hybrid closed-loop system contributed to the participant discontinuing the CamAPS FX intervention 17 days after randomisation and resuming her prior Tandem Control IQ hybrid closed-loop system. The other events were related to components of the hybrid closed-loop system rather than the algorithm themselves: insulin pump set failures, CGM sensor issues or a coincidence of the two.

Table 2.18 Safety outcomes

	Hybrid closed-loop	Standard care
Severe Hypoglycaemia		
Number of events	6	5
Participants with ≥1 event	4	5
Incidence per 100 person years	20.8	16.4
Severe Hyperglycaemia / Ketosis		
Number of events	34	8
Mild-moderate[α]	8	5
Severe[β]	25	2
DKA[δ]	1	1
Participants with ≥1 event	11	6
Participants with 1 event	8	5
Participants with ≥2 events	3	1
DKA incidence per 100 person years	3.5	3.3
Serious Adverse Events[ϕ]		
Total number of events	34	14
Hyperglycaemia / Ketosis	22	3
Hypoglycaemia	3	1
Other	9	10
Participants with ≥1 event	10	9
Incidence per 100 person years	118.1	45.9
Adverse Device Events: Hybrid closed-loop		
Number of events[λ]	7	N/A
Participants with ≥1 event	7	N/A
Incidence per 100 person years	24.3	N/A
Adverse Device Events: CGM		
Number of events	7	9
Participants with ≥1 event	7	7
Incidence per 100 person years	24.3	29.5

CGM = Continuous glucose monitoring

α Mild -moderate includes self-treated ketosis (ketones > 0.5mmol/L) which resolved without hospital admission.

β Severe ketosis plasma ketones > 1.0mmol/L, requiring hospital admission and treatment with intravenous insulin. One participant had 20 events none of which occurred whilst using hybrid closed-loop therapy (though assigned to the intervention arm).

δ DKA: Diabetic ketoacidosis was defined as ketosis, acidosis and treatment with fixed rate intravenous insulin infusion.

ϕ Serious adverse events are adverse events that led to death; serious deterioration in health; life-threatening illness or injury, permanent impairment, in-patient or prolonged hospitalisation, fetal distress, death or congenital anomaly.

λ Seven hybrid closed-loop adverse device events included an incorrect insulin bolus with severe hypoglycaemia post miscarriage, one hyperglycaemia which contributed to a participant stopping CamAPS FX hybrid closed-loop treatment day 17 post randomisation, and one moderate ketosis event following loss of Bluetooth connectivity overnight on the day leading into admission for preterm birth. Other events relating to sensor and/or infusion set failures were non-serious (additional details in Table 2.19).

Table 2.19 Adverse device events

Related to HCL[α]	Related to CGM[α]	SAE?	Event	Severity	Notes
Possibly	Unlikely	No	Hyperglycaemia: highest glucose 14.4mmol/L	Mild	Device deficiency – CamAPS app required re-installation. Participant reported anxiety, nausea, and lethargy (unrelated to device). No impact on pregnancy outcome.
Probably	Unlikely	**Yes**	Severe Hypoglycaemia (post miscarriage, known epilepsy: stress, sleep deprivation)	Severe	Closed-loop 'user error' reported – participant forgot to change her insulin carbohydrate ratio and gave incorrect bolus dose post-miscarriage. Post miscarriage ADE – no impact on pregnancy outcome.
Possibly	Unrelated	No	Self-treated hypoglycaemia: lowest glucose 2.9mmol/L	Mild	Resolved prior to admission for COVID infection with abdominal pain/vomiting. No impact on pregnancy outcome.
Unrelated	Definitely	No	Dermatitis allergic	Mild	No impact on glycaemic / pregnancy outcome.
Definitely	Unrelated	No	Moderate non-acidotic ketosis: Ketones 2.5, glucose 17.8mmol/L, pH 7.4, bicarb 14.1. Spontaneous onset of preterm labour	Moderate	Closed-loop went out of Auto Mode (loss of Bluetooth connectivity) whilst asleep. Auto-mode reconnected when she woke and closed-loop was reinstated. Admitted later same day with preterm labour at 35+2 weeks' gestation and was delivered by repeat caesarean section (as had been planned for elective caesarean section for previous caesarean section) Participant was seen for reduced fetal movements on the day before ADE but a potential impact on pregnancy outcome cannot be excluded.
Unrelated	Definitely	No	Sensor bled at insertion site. Settled with compression.	Mild	No impact on glycaemic/pregnancy outcome
Unrelated	Definitely	No	Bruising at sensor insertion site.	Mild	No impact on glycaemic/pregnancy outcome
Unrelated	Definitely	No	Sensor bled at insertion site. Sensor replaced	Mild	No impact on glycaemic/pregnancy outcome
Probably	Definitely	No	Hyperglycaemia: highest glucose 17.8mmol/L	Moderate	Sensor failed to report glucose levels from 4am whilst sleeping. The pump continued to deliver insulin but did not adequately control glucose levels, resulting in discontinuation of her assigned CamAPS FX HCL treatment. Participant resumed her prior Tandem control IQ closed-loop system 17 days post-device training.
Unrelated	Possibly	**Yes**	Hyperglycaemia: highest glucose 20.1mmol/L. Moderate non-acidotic ketosis: Ketones 3.3. pH 7.4, Bicarb 17	Moderate	Sensor stopped working intermittently 28 days after randomization. Moderate non-acidotic ketosis - admitted and treated with variable rate iv insulin infusion. No impact on pregnancy outcome

Definitely	Definitely	No	Mild ketosis: Ketones 0.7, resolved at presentation to A&E, not admitted	Moderate	Hyperglycaemia induced by set failure compounded by loss of glucose sensing ~3 hrs. Resolved once glucose sensing and hybrid closed-loop recommenced. No impact on pregnancy outcome
Definitely	Unrelated	No	Mild ketosis. Hyperglycaemia – highest glucose 21.7mmol/L. Medium urinary ketones. Not admitted.	Moderate	Participant reported sensor came loose and infusion cannula set kinked – pump did not alert participant. No impact on pregnancy outcome

HCL = hybrid closed-loop, CGM = continuous glucose monitor, SAE = serious adverse event, ADE = adverse device event
α Relation to investigational medical device: possibly, probably, or definitely related (or unlikely / unrelated) to device as determined by local site investigator

2.6 Discussion

We found that the percentage of time that glucose levels were within the pregnancy-specific target range of 3.5-7.8mmol/l from 16 weeks' gestation until delivery was 10.5% higher (an additional 2.5 hours per day) in participants assigned to hybrid closed-loop, compared to those assigned to continuous glucose monitoring alongside their usual insulin delivery method. The maternal glycaemic benefits were achieved by reducing maternal hyperglycaemia and increasing nocturnal time spent in pregnancy-specific target range. Improvements in glucose outcomes were consistent across baseline maternal age, glycaemic categories, clinical site and pre-trial insulin delivery method. Furthermore, there was no increase in gestational weight gain or maternal insulin doses. The incidence of hypoglycaemia was low at baseline, and apart from night-time reductions, did not differ between groups. A five-percentage point increased time spent in pregnancy-specific target range was apparent by the end of the first trimester, suggesting that the benefits occurred soon after hybrid closed-loop initiation (~12 weeks' gestation), which is crucially important for women and clinicians considering therapeutic changes during early pregnancy.

The trial was conducted during the COVID-19 pandemic, which particularly impacted pregnant women, and necessitated rapid implementation of virtual training and visits. Nonetheless, hybrid closed-loop usage was high (>95%) throughout pregnancy, and without apparent safety problems, including among those new to insulin pump therapy. Participants who continued standard care had more clinic visits and more unscheduled contacts, suggesting that beyond the initial training session (typically ~2 hours duration), hybrid closed-loop use did not require additional healthcare professional input.

Recent trials have demonstrated the benefits of hybrid closed-loop therapy to those with newly diagnosed type 1 diabetes and young children, and these results extend the evidence to pregnant women (114,115). Alongside women's motivation to minimise pregnancy complications, hybrid closed-loop facilitated attainment of the International Consensus on Time in Range CGM sensor glucose target of 70% time in pregnancy-specific target range. Given the rapid increases in time in pregnancy-specific target range observed within one week of therapy initiation in this trial, we speculate that further benefits may be obtained from starting hybrid closed-loop before pregnancy, or as soon as possible, after pregnancy is

confirmed. Participants were offered the option to continue hybrid closed-loop during the inpatient admission for labour and delivery, this will be reported separately.

The current trial participants gained an additional 10% time in pregnancy-specific target range above and beyond the 10% increment achieved by continuous glucose monitoring and standard insulin therapy across pregnancy. Previous studies demonstrated that every 5% increased time in range is associated with improved obstetric and neonatal outcomes (64). Our trial was not powered for pregnancy outcomes, but we infer that this additional 10% time in the pregnancy target range would be expected to have additional health benefits for mothers and their babies.

Strengths of our trial include its parallel-group, randomised controlled design, generalisability of our patient population, including those naïve to insulin pump therapy, a large proportion who initiated therapy during the first trimester and a flexible trial protocol that facilitated virtual or in-person visits. There was no evidence of increased clinical contacts, which is frequently observed in investigational device trials.

This trial had certain limitations. The current sample size did not provide definitive data on maternal and neonatal health outcomes. The majority of participants were from a White ethnic background (93%), 56% had undergraduate university or equivalent education and those who did not reach a HbA1c ≤86mmol/mol by randomisation were excluded. First trimester data are limited because participants were randomised at a median of 11 weeks' gestation. Furthermore, owing to differences between different hybrid closed-loop systems, these data and results cannot be extrapolated to systems with higher glucose targets.

In this study, use of hybrid closed-loop provided an additional clinical advantage beyond that which can be achieved by continuous glucose monitoring and insulin pump therapy and supports proposed NICE guideline recommendations that hybrid closed-loop therapy should be offered to all pregnant women with type 1 diabetes.

In conclusion, hybrid closed-loop use was effective in pregnancy complicated by type 1 diabetes and able to accommodate the marked gestational changes in insulin doses in study participants.

Chapter 3: Psychosocial results of the AiDAPT trial

3.1 Chapter Introduction

Chapter 2 outlines the main biomedical analyses from the AiDAPT (**A**utomated **I**nsulin **D**elivery **A**mong **P**regnant women with **T**ype 1 diabetes) study examining hybrid closed-loop therapy in type 1 diabetes pregnancy. This chapter presents the associated psychosocial studies and assessments exploring women's experiences of the use of hybrid closed-loop therapy as well as the perspectives of AiDAPT trial healthcare professionals who cared for and clinically supported the participants' use of hybrid closed-loop therapy during their pregnancies.

3.2 Chapter Summary

Background: As well as glycaemic benefits of hybrid closed-loop systems, previous studies have reported psychosocial and quality-of-life benefits to people with type 1 diabetes. If more widespread use of hybrid closed-loop therapy in type 1 diabetes pregnancy is to be adopted, it is increasingly recognised that the experiences and views of the stakeholders: the women themselves and the healthcare teams that will train and support them, are taken into account.

Methods: This chapter comprises of three inter-related studies. The first was the patient-reported outcomes, evaluated using validated questionnaires, in early and late pregnancy among 116 AiDAPT trial participants from both the intervention (hybrid closed-loop) and standard care arms. The second was the qualitative interviews of 23 women from the hybrid closed-loop intervention arm performed just after randomisation and approximately 20 weeks later. The third was the qualitative interviews of 19 healthcare professionals involved in delivering the study and supporting trial participants including those randomised to hybrid closed-loop therapy.

Results: Women and healthcare professionals described both glycaemic and quality-of-life benefits associated with using hybrid closed-loop therapy during pregnancy. These included alleviation of some of the workload of diabetes self-management, less worry, better sleep and feeling 'more normal'. The use of hybrid closed-loop therapy also enabled women and healthcare professionals to build more trusting and effective therapeutic relationships which further improved women's pregnancy experiences. Both groups acknowledged that work was still required to benefit optimally from hybrid closed-loop use, and that this work was most effectively achieved by a three-way collaboration between the woman, the healthcare

team and the technology itself. Healthcare professionals developed the view that all women should be offered this technology, if wider provision and access was granted, as clinical and psychosocial benefits were gained by all. They also stated that although there would be initial challenges to ensure robust development of services and equity of hybrid closed-loop use in type 1 diabetes pregnancy across the country, this would be worth the effort.
Conclusions: Hybrid closed-loop has wide ranging quality-of-life benefits and can facilitate positive pregnancy experiences. Optimal use of this technology requires close collaboration between the pregnant woman, diabetes and maternity healthcare teams and the hybrid closed-loop system . Despite initial workforce challenges, healthcare professionals recommend that the CamAPS FX hybrid closed-loop system be offered to all pregnant women with type 1 diabetes.

3.3 Background

3.3.1 The lived experience of women with type 1 diabetes during pregnancy

Type 1 diabetes glycaemic targets are more stringent during pregnancy compared to outside of pregnancy in order to reduce risks of obstetric and neonatal complications. In addition, gestational changes in insulin resistance, insulin pharmacokinetics and increased day-to-day variability make managing optimal glycaemia and achieving these stringent glycaemic targets more challenging (16–18,27–29). Understandably, these challenges increase the daily burden of women's usual 24/7 diabetes self-management and together with the additional worry about the pregnancy and baby's wellbeing, pregnant women frequently describe increased diabetes distress and overall mental burden (116,117).

Several studies have explored the lived experiences of women with type 1 diabetes in pregnancy. Given the associated complications, pregnancies in women with type 1 diabetes are considered "high risk" and require more intensive obstetric follow up and intervention. Women often felt they were unable to "forget" that they had diabetes: *"You're told about the risks at once"*; with the increased specialist medical involvement (in addition or instead of usual midwifery or antenatal care) and increased medicalisation of their pregnancy. This subsequently impacted on their ability to enjoy pregnancy and to some led to a detachment from their pregnancy (31,116,118–122).

"Mentally, I have hardly known that I was pregnant. I never really entered into pregnancy. ...It has only been blood sugar. Even though I feel that it kicks a bit and I can see it on the ultrasound monitor, I find it difficult to get it into my head that I'm pregnant." (119)

They also described the resentment or frustration that their diabetes limited or influenced the decisions that they were able to make with respect to pregnancy choices (118).

"What I mostly wish, is that I carry the baby to full term and that I would have a normal delivery… It would be so exciting if the diabetes is one thing on its own and now I'm going to give birth, not that I give birth because of the diabetes." (118)

Some women also described the feeling of being different and isolated, especially when comparing their experiences to pregnant women without diabetes (119,123).

When I talk to my friends who also have children, they can complain a lot about having had troublesome pregnancies, and so on. Of course, that's how they feel, isn't it, but you're quite alone, aren't you....as a pregnant diabetic? (123)

Women frequently described how much work and discipline it took to strive for the tight pregnancy glycaemic targets in order to minimise maternal and fetal risks, with some likening it to a "full time job" (31). This, together with the acute awareness of the degree to which their baby's wellbeing and development is linked to their glycaemia and the feeling of "being controlled by blood glucose levels for the child's sake" often resulting in feelings of exaggerated responsibility, constant worry, guilt and overall increased anxiety and mental burden (31,118,122–127).

"I decided to give up work before I had children, because of the immense amounts of pressure to try and keep everything controlled and everything so tight." (125)

"The blood sugar controls everything… I always have to take a blood sample before I do anything… It is because I am pregnant, it is on my mind all the time, asleep as well as awake." (118)

"Honestly, you have to make changes every single day and you're having so many lows, so I feel like diabetes was kind of like the forefront of everything in my pregnancy and worrying about it because I was diabetic." (122)

"… You easily feel guilty when you have got diabetes. If anything's wrong with the child or if something had shown up at the ultrasound, you would easily have blamed yourself a lot." (118)

In terms of their diabetes self-management, women described an increased fear of hypoglycaemia in the pursuit of optimal glycaemia (122,123,125).

"And sometimes in the evenings I was like...I don't know if I dare go to bed, what if I die in my sleep and my husband doesn't notice anything? That really gives you a lot of anxiety, you don't know how you're going to survive." (123)

Together with the feeling of being different along with exaggerated responsibility and increased mental burden often led to feelings of loneliness which persisted even when support from family, friends and healthcare professionals was strong and appropriate (118). However, in spite of these psychosocial challenges and increased mental burden and pressure, the desire for a healthy pregnancy and baby is a strong motivator for the majority of women (118,125,127). Women who were able to come to some acceptance of and "master" the challenges of diabetes self-management during pregnancy and felt well supported by friends, family, healthcare professionals and employers to do so did describe an improvement in wellbeing rather than feeling "enslaved" by their condition (119).

3.3.2 The role of the healthcare professional and women's experiences of diabetes-maternity care provision

Healthcare professionals working in diabetes play a role in facilitating access to diabetes technologies, including hybrid closed-loop therapy, at a service delivery level (128,129). Their role when providing training and clinical and technical support for the use of diabetes technologies can also strongly influence a person with diabetes' ongoing use and relationship with that technology (130,131). However, studies exploring the perspectives of healthcare professionals who have supported hybrid closed-loop use in pregnancy are limited to the early generation hybrid closed-loop systems, that required substantially more input from users and healthcare teams (132,133).

Previous studies explored the perception of the role of the health care professional and experience of maternity health services from women with diabetes. In some cases, the additional follow up, attention received during pregnancy via specialist antenatal clinics provided women with a sense of being prioritised by the healthcare system compared to usual adult diabetes services. When received, the acknowledgement of the intensive nature of diabetes self-care and provision of additional support (for example facilitation of sick leave) in order to prioritise and achieve optimal glycaemia was noted by women with surprise and appreciation (123). However, for some women the frequent attendance with more appointments compared to the low risk maternity population had a negative impact when also balancing employment and childcare (31,120,127).

"My work schedule interferes. I work full-time, which can bring its own stressors. It definitely takes away time that I could be using to take care of myself…between all the

doctor's appointments and missing work… and having poor compensation is an added stressor for sure." (127)

Women also identified division of care difficult describing a feeling of "being lost in the healthcare system", especially when aspects of antenatal care were delivered by professionals without expertise in diabetes for example community or primary midwifery care and around labour and delivery (31,122,123,125).

"My midwife would make the same recommendation several times, for instance that I should take my iron tablets with a glass of juice. And I told her I couldn't do that. So we went out and took my blood count and it was a bit low and then she repeated it, 'Take your iron with some juice.', and I said, 'I still can't do that because my blood glucose will go over the top.', and then she said, 'Oh, yes, right!'" (123)

"I went for bloodwork during pregnancy and I was six months pregnant. And the lady at the clinic told me, like 'Aren't you worried that your baby is going to have diabetes because you have diabetes?'. There were people that are just very ignorant about things. And I remember leaving there crying, because I'm six months pregnant, there's really nothing I could do about it. And also it's not helpful." (122)

In these cases, some women felt like they had to become a "messenger" between their healthcare providers and an expert in their own condition as they felt unable to trust the competence and knowledge of professionals when receiving conflicting or competing advice (121,123,125).

Some women described the balance between being in control of their own diabetes self-management versus "a need to surrender responsibility" to healthcare professionals (119). The relationship between the woman and the healthcare professional affected the degree to which women felt in control of their pregnancy and diabetes self-management as well as the degree of worry they experienced during pregnancy. Women who felt controlled by their healthcare professionals felt more alone and less in control (119,122,123,125,127). When this therapeutic relationship, between healthcare professional and woman, was instead comfortable and trusting, and where women felt they were seen more holistically as a person

rather than being defined by their glycaemia, women felt more empowered to work and improve on their diabetes self-management (121,125,127,134).

"Each consultation you go to can be stressful and can knock your confidence when it's something you're dealing with on a daily basis. You need confidence and self belief. If they [healthcare professionals] can admit that your results are good, or even that your results are satisfactory compared to what they were, that gives you confidence" (134)

As well as providing information on their condition and its management in pregnancy, healthcare professionals who provided both psychological and clinical support to the women, helping them to cope and work with them to manage problems encountered were found to be most valuable to women (31,121,127,134,135).

"She said: "I know that I have to be like this with you." And then it felt like, wow, you know me. It was so awesome that she could put into words and had found who I was in a caring situation." (31)

3.3.3 Women's experience of hybrid closed-loop therapy in pregnancy

There have been five previous studies exploring women's experience of using hybrid closed-loop therapy in pregnancy (Table 3.1). Two reported the psychosocial outcomes of the two UK Closed-Loop in Pregnancy (CLIP-03, CLIP-04) studies which examined previous prototype versions of the CamAPS FX system (86,87,136,137). The third from Canada examined the off-label use of the Tandem Control-IQ system during pregnancy and a further two studies from France and Slovenia, examined the off-label use of Medtronic MiniMed 780G hybrid closed-loop system in pregnancy (99,101,105). Data collection varied including the use of patient-reported outcomes, questionnaires and qualitative interviews.

Table 3.1 Qualitative studies evaluating the lived experience of hybrid closed-loop use during type 1 diabetes pregnancy

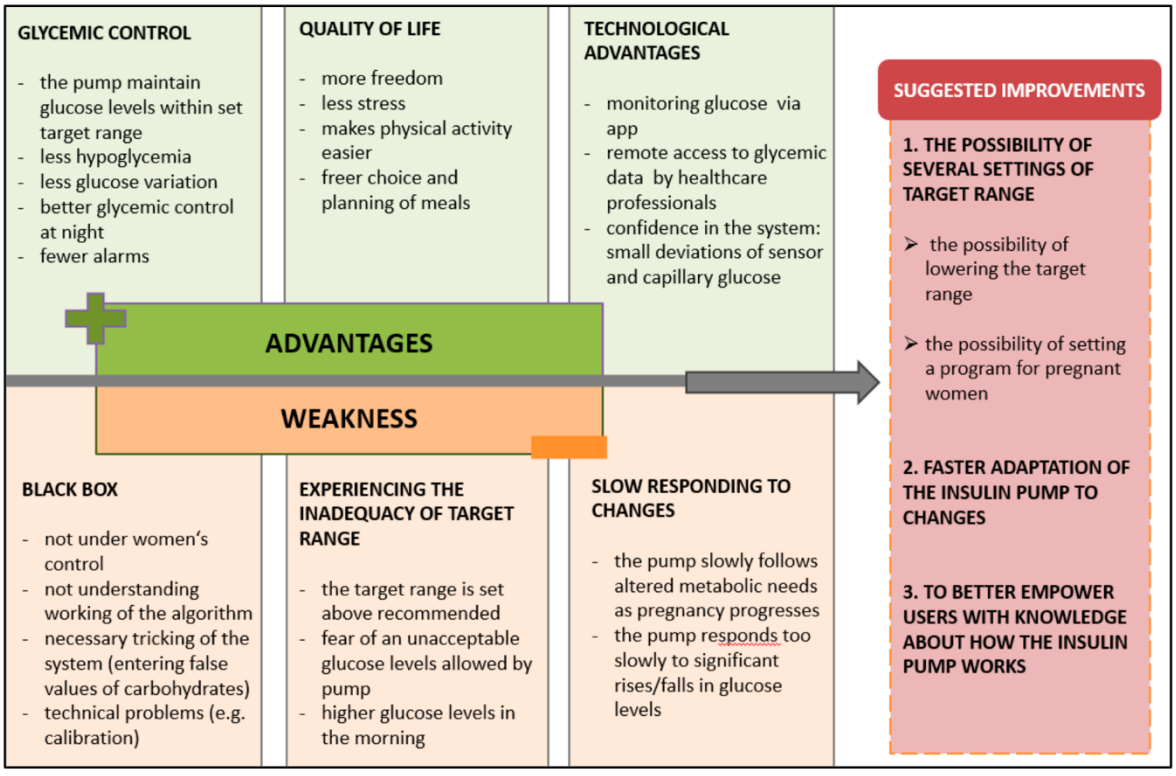
Study*	**Number of participants and HCL[α] system**	**Qualitative outcomes assessed**	**Patient-reported outcomes**
Farrington et al 2017 (CLIP-03 study participants) (136)	N = 16 HCL (Prototype CamAPS FX) Crossover study: all participants completed 4 weeks overnight HCL and 4 weeks day-and-night open-loop insulin pump therapy	Questionnaires - Diabetes Technology Questionnaire (138) - Hypoglycaemia Fear Survey (108) Semi-structured Interviews	No differences between overnight HCL and open-loop insulin pump phases on the Diabetes Technology Questionnaire or Hypoglycaemia Fear Survey (either as a total score or on either behaviour or worry subscale).
Stewart et al 2018 (Patient-reported outcomes of the CLIP-04 study) (87)	N = 16 HCL (Prototype CamAPS FX) Crossover study: all participants completed 4 weeks HCL and 4 weeks open-loop insulin pump therapy	Questionnaires - Diabetes Technology Questionnaire - Hypoglycaemia Fear Survey - Pittsburgh Sleep Quality Index (109)	• No difference between HCL and open-loop insulin pump phases for Diabetes Technology Questionnaire • Less fear of nocturnal hypoglycaemia: >80% at the end of both phases. But over one-third reported ongoing worry or fear about hypoglycaemia during sleep. • No difference in quality of sleep during both phases.
Farrington et al 2018 (CLIP-04 study participants) (137)	N = 16 HCL (Prototype CamAPS FX)	Semi-structured Interviews	n/a
Wang et al 2022 (Canada) (101)	N = 4 HCL (Tandem Control IQ)	Semi-structured Interviews	n/a
Munda et al 2022 (Slovenia) (99)	N = 6 HCL (Medtronic MiniMed 780G)	Non validated questionnaire with ten open-ended questions	n/a
Guibert et al 2023 (France) (105)	N = 13 HCL (Medtronic MiniMed 780G)	Non validated questionnaire with four open-ended questions	n/a

***** CLIP = Closed-Loop in Pregnancy studies

[α] HCL = hybrid closed-loop therapy

In both CLIP-03 and CLIP-04, there were no statistically significant differences in the patient-reported outcomes between the open-loop insulin pump therapy and hybrid closed-loop phases when compared with baseline (87,136). However, semi-structured interviews highlighted both benefits and burdens of these early generation hybrid closed-loop prototypes. Benefits included less worry about sleep; improved glycaemic control; facilitating more flexibility in food choices and engaging in physical activity, less stigma when going out, and more control over and "time off" from diabetes (99,101,105,136,137). As with any treatment, women also described burdens such as technology glitches; the impact of safety alarms; impact on lifestyle including clothing choices; increase and in some cases overwhelming amounts of data; increase needs to maintain use of hybrid closed-loop and worry of dependency on the system and deskilling of diabetes self-management (136,137). The Slovenian study also captured concerns specific to the off-label use in pregnancy of the Medtronic MiniMed 780G hybrid closed-loop system related to the "inadequacy of the target range" and "necessary tricking of the system" (Figure 3.1) (99).

Figure 3.1 Women's experience of the off-label use of Medtronic 780G hybrid closed-loop system in type 1 diabetes pregnancy
(reproduced from Munda et al 2022) (99)



These studies, whilst helpful in starting to reflect the wider benefits of hybrid-closed-loop use, are limited by the small numbers of more highly selected (early adopter) participants and evaluation of early generation prototype hybrid closed-loop systems, often used for shorter durations during pregnancy.

This chapter presents the psychosocial assessments of and semi-structed interviews with AiDAPT trial participants, and semi-structured interviews with the study staff who supported the provision hybrid closed-loop therapy and its use during the study. These aim to capture the views and lived experiences of using hybrid closed-loop therapy in pregnancy and to identify and highlight any recommendations and challenges that would be helpful to support the training and use of hybrid closed-loop technology during pregnancy in routine clinical care.

3.4 Methods

3.4.1 Women's lived experiences and patient-reported outcomes

The AiDAPT (**A**utomated **I**nsulin **D**elivery **A**mong **P**regnant women with **T**ype 1 diabetes) study is a multicentre randomised controlled trial which compared hybrid closed-loop therapy with standard insulin therapy. Pregnant women with type 1 diabetes across nine UK NHS sites were recruited and randomly assigned to receive the intervention hybrid closed-loop system (CamAPS FX system) or to standard care: continuation of their standard insulin therapy (multiple daily injections on insulin pump) together with continuous glucose monitoring (CGM). Participants continued their assigned treatment for the duration of pregnancy until delivery. All participants were asked to complete validated questionnaires in early and late pregnancy. Participants who were randomised to the intervention (hybrid closed-loop) arm were given the option to participate in interviews with the AiDAPT qualitative interview team. Further details are available in the study protocol, included in the appendices of this thesis, and Chapter 2. Both the protocol and main study results have been previously published (83,139). Research Ethics Committee approval and trial registration for this interview study were included as part of the main AiDAPT trial (Cambridge Central Research Ethics Committee: 18/EE/0084 and ISRCTN56898625) (83).

Patient-reported outcomes

At baseline (approximately 12 weeks' gestation), all participants were asked to complete the following validated questionnaires; Euroqol Five Dimensions Health-Related Quality of Life Questionnaire (EQ-5D-5L), Diabetes Distress Scale, Hypoglycaemia Fear Survey II (worry scale only), and Pittsburgh Sleep Quality Index (106–109). Hybrid closed-loop intervention arm participants, were asked to complete an additional INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) questionnaire (110). Participants were requested to repeat baseline questionnaires at 34-36 weeks. The relevant permissions were sought and received for all questionnaires during study protocol development and examples of these questionnaires are included in the appendix of this thesis.

The EQ-5D-5L Health-Related Quality of Life Questionnaire explores current health, both positive in terms of well-being and negative in terms of illness (106). It is assessed firstly descriptively in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A further visual analogue scale assesses the responder's self-rated health. The utility score is an expression of the Quality Adjusted Life Years (QALY) and is adjusted according to country of origin, with a maximum score of 1 indicating the best health state. The Diabetes Distress Scale comprises of 17 items and assesses worries and concerns related to diabetes and its management (107). Four subdomains, in addition to a total score, provide detailed assessments of emotional burden, physician-related distress, regimen-related distress, and diabetes-related interpersonal distress. Higher scores reflect higher levels of diabetes distress. The Hypoglycaemia Fear Survey Questionnaire II comprises of two subscales, one for behaviour and one for worry (108). In this study, only the 13-item "worry subscale" was used which measures anxiety and fear. Higher scores indicate higher fear of hypoglycaemia. The Pittsburgh Sleep Quality Index is a 19-item questionnaire that holistically assesses sleep quality and sleep duration over the preceding month (109). Higher scores indicates worse sleep quality. The INSPIRE questionnaire evaluates the impact of hybrid closed-loop systems on the responder's psychosocial functioning, diabetes self-management, health, usability, wearability and burden (110). Higher scores indicate more positive experiences with hybrid closed-loop therapy.

Qualitative interviews

At recruitment, all women who participated in the AiDAPT trial were given the option of consenting to the interview study. Those who were randomised to the hybrid closed-loop

intervention arm of the study were sampled for interview. Purposive sampling was used to ensure optimal diversity with respect to the categories of socioeconomic status, age and parity. Recruitment continued until data saturation was reached.

Women were interviewed twice: after randomisation to hybrid closed-loop therapy and approximately 20 weeks later in pregnancy. Interviews were conducted by an independent experienced, non-clinical qualitative researcher (Dr David Rankin, Edinburgh Qualitative Health Research Group, Scotland) who had no prior relationship with participants. Interviews were conducted over the telephone and were digitally recorded and transcribed. They lasted between one to two hours. Semi-structured interviews were performed according to a topic guide (Table 3.2), which was developed by the qualitative team based on their previous experience of exploring and reporting user experience of hybrid closed-loop use (140–142). At baseline, women were asked about what their previous experiences were of managing diabetes before commencing hybrid closed-loop therapy and also any previous experiences of managing diabetes in pregnancy. The topic guides were then used to structure interviews around topics that were felt important to cover and also trigger any other aspects participants wished to raise.

Table 3.2 Topics explored in interviews with women
(relevant to the analysis, adapted from Lawton et al 2023) (143)
HCL = hybrid closed-loop

Background information and pre-trial experiences

- Age, occupation, living arrangements, number and age of other children.
- Diabetes duration and diabetes devices (e.g., pump, multiple daily injections, continuous glucose monitoring, finger pricks) used pre-trial.
- Views, hopes and concerns about managing diabetes while pregnant and related pregnancy/health impacts.
- Experiences of managing diabetes during previous pregnancies (if any) and/or current pregnancy before joining the trial, including:
    - Regimen used (insulin administration and glucose monitoring); adjustments to basal rates/background and insulin-to-carbohydrate ratios; dietary choices and managing diabetes at mealtimes; undertaking physical activity; attainment of pregnancy glucose targets.
    - Management of and worries/concerns about hypo- and hyperglycaemia.

Impact of regimen used on everyday life (e.g., sleep, work/family/social life) and overall pregnancy experience

- Experiences of and views about receiving support from healthcare professionals during previous pregnancies and/or pre-pregnancy planning.

Experiences of using the hybrid closed-loop (HCL) system during the trial

- Experiences of initial HCL training and education, learning to use and adapting to HCL; developing confidence and trust in HCL; any concerns about using HCL (and components) during the trial.
- Experiences of and views about using the HCL to manage diabetes while pregnant, including:
    - Use of the app to inform decisions about diabetes management tasks (e.g., calculating/administering mealtime bolus doses, managing/treating hypo- and hyperglycaemia).
    - Use of 'Boost' and 'Ease-off' functions; use of corrective doses of insulin.
    - Impact of CL use when physically active.
    - Ability to attain (and maintain) pregnancy glucose targets.
    - Impact of HCL use on worries/concerns about hypo- and hyperglycaemia.
    - Engagement with and access to insulin and glucose data via app on phone (and if and how this changed over time); which of the available data participants used; if/how data access affected how they managed diabetes.
    - Perceived impact of HCL use on everyday life (e.g. sleep, work/family/social life)
- Impact of HCL use on worries and concerns about managing diabetes while pregnant and related pregnancy and health outcomes.
- Experiences of and views about contact and support received from healthcare professionals (e.g., mode and frequency of, and reasons for, contacts; impact of HCL use on participants' experience of healthcare encounters and interactions)
- Experiences of and views about healthcare professionals having remote access to their real-time glucose and insulin data (e.g. concerns, perceived (dis)advantages).

3.4.2 Healthcare professionals' views

During the AiDAPT trial, healthcare professionals involved in the delivery of the study received training in the use of the study hybrid closed-loop system and associated devices (CGM and insulin pump). Device and technology training for hybrid closed-loop intervention arm participants was then led by the research educator and supported by local healthcare professionals at sites. These healthcare professionals then provided ongoing technological support to participants in addition to providing their routine clinical antenatal care. Research Ethics Committee approval and trial registration for an associated study exploring healthcare professionals' views on the use of hybrid closed-loop therapy in pregnancy was included as part of the main AiDAPT trial (83).

Healthcare professionals with at least six months' experience in supporting hybrid closed-loop use during pregnancy were recruited from across eight sites. Purposive sampling was used to ensure individuals were heavily involved in providing hybrid closed-loop care and support to women were included and that there was diversity across different grades and roles of staff. Recruitment continued until data saturation was reached.

Semi-structured interviews lasted one to two hours and were conducted over the telephone by an independent experienced, non-clinical qualitative researcher (Dr David Rankin, Edinburgh Qualitative Health Research Group, Scotland). A topic guide (Table 3.3) was used to inform interviews. It was developed by the qualitative interview team based on previous research into healthcare professionals' views on hybrid closed-loop use and discussion with clinical colleagues (148–150). The guide was revised between interviews to take into account new or previously unidentified topics.

Table 3.3 Topics explored in interviews with healthcare professionals
(relevant to the analysis, adapted from Lawton et al 2023 and Rankin et al 2023) (144,145)
HCL = hybrid closed-loop

- Participants' clinical background, training and experience; previous involvement (if any) in trials of HCL technology or supporting HCL users receiving routine care.
- Experiences (if any) of training study participants to use the HCL.
- Experiences of providing support to participants using an HCL during pregnancy; perceived differences in the type and amount of support required compared with people using conventional insulin regimens (e.g. continuous glucose monitoring with pump and/or multiple daily injections); perceived sustainability of providing this level of support upon rollout.
- Perceived benefits and drawbacks of using HCL technology compared to other regimens used to manage type 1 diabetes in pregnancy.
- Experiences of training and support received to deliver the trial; views about the kinds of training, support and resources healthcare professionals will need to support HCL users in routine clinical care.
- Views about who should provide and how services should be organised or structured to deliver HCL therapy in routine clinical care.
- Perceived impact of rolling out HCL technology on healthcare professionals' clinical practice, workloads and wider healthcare resources.

3.4.3 Qualitative interview data analysis

Qualitative interview data analysis for both the women's and healthcare professionals' qualitative interviews were performed by the AiDAPT qualitative interview team. This group was comprised of five experienced, non-clinical researchers from The Usher Institute, Edinburgh Qualitative Health Research Group, University of Edinburgh.

Data from each group (AiDAPT trial participants and healthcare professionals) were analysed using qualitative descriptive and thematic analysis in order to allow for both a priori and emergent interests to be identified (146–148). The AiDAPT qualitative interview team first analysed the data by "constant comparison". This involved multiple read throughs of transcripts and then identifying common themes within each group of interviews. A coding frame for each group was agreed upon by researchers in the AiDAPT qualitative interview team and used to capture all relevant topics. NVivo qualitative analysis software (QSR International, Doncaster, Australia) was used to facilitate data coding and retrieval.

A further online workshop was held in September 2022 to discuss preliminary interview findings from the healthcare professional interviews with a wider sample of stakeholders:

principal investigators, other healthcare professionals involved in the study, other non-clinical trial staff and members of the qualitative research team. The aim was to generate a set of practical and relevant set of recommendations and highlight any challenges that could be used to inform a potential national rollout of hybrid closed-loop use in pregnancy. A "What? So What Now What?" approach was used and individuals who were unable to attend the meeting were corresponded with via email in order to contribute to the recommendations (149).

3.5 Results

Women's lived experiences

Twenty-three women from seven clinical sites were interviewed between April 2020 and April 2022. Their characteristics are presented in Table 3.4. The majority were White British (91%), married or co-habiting (87%) with more than 80% being in full-time or part-time employment. Half of the women interviewed in this qualitative study self-reported using multiple daily injections prior to recruitment. The two intervention participants who were using hybrid closed-loop therapy at baseline of the AiDAPT study were not interviewed. Multiple pregnancies were not excluded from the AiDAPT study but all women recruited to AiDAPT were carrying singleton pregnancies.

Topics discussed by the women through the qualitative interviews were categorised into two groups:

1. Previous experiences of pregnancy with type 1 diabetes
2. Experiences of using hybrid closed-loop therapy during pregnancy

When describing their lived experience of previous pregnancies (prior to the pregnancy involved in the AiDAPT trial), women talked about the physical, mental and emotional challenges to diabetes self-management. They also were able to reflect on the limitations of the tools available to them in those pregnancies compared to hybrid closed-loop therapy (Table 3.5).

When describing their experience of using the hybrid closed-loop during pregnancy, women described two phases: the first was the initial phase of a few weeks adjusting and learning how the hybrid closed-loop system integrates with and could help unburden some of their existing diabetes self-management. Part of this also involved an adjustment in their

therapeutic relationship with healthcare professionals, namely the increased availability of more detailed insulin and glucose data to healthcare teams and how initial intensive oversight and emotional support helped develop and fast-track confidence in the system and integration into their diabetes self-management.

Table 3.4 Participant characteristics

N=23 pregnant women with type 1 diabetes (adapted from Lawton et al 2023) (143)

Baseline Characteristics	**N**	**%[α]**	**Mean, SD, (range)**
Married/co-habiting	20	87.0	
Employment			
Full-time	10	43.5	
Part-time	9	39.1	
Unemployed/student	2	8.7	
Full-time mother	2	8.7	
Occupation[β]			
Professional	8	34.8	
Semi-skilled	6	26.1	
Unskilled	6	26.1	
Full-time mother/carer	2	8.7	
Student	1	4.3	
Ethnicity			
White, British	21	91.3	
White, other nationality	2	8.7	
Characteristics at the time of interview			
Age at time of interview : years			31.5 ± 4.6 (22 - 39)
Number of previous pregnancies			1.3 ± 1.2 (0 - 5)
Diabetes duration; years since diagnosis			18.6 ± 6.8 (2 - 28)
Baseline HbA1c (mmol/mol)			59 ± 10.6 (48 - 90)
Diabetes management used before current pregnancy			
Insulin regimen:			
Multiple daily injections	12	52.2	
Insulin pump	11	47.8	
Self-reported glucose monitoring:			
Finger-prick testing	10[δ]	43.5	
Freestyle Libre 1	7	30.4	
Freestyle Libre 2	2	8.7	
Real-time CGM	4	17.4	

SD = standard deviation

α Percentages may not add up to 100% due to rounding.

β Defined using the International Standard Classification of Occupations 2008 (ISCO-08)

δ Seven of these women (30.4%) were given use of a sensor (in most cases, Freestyle Libre 1) near the start of their current pregnancy, i.e. shortly before joining the AiDAPT trial.

Following this phase, women described the maintenance phase of ongoing learning whilst being able to enjoy the benefits of hybrid closed-loop use: better glycaemia; less worry and anxiety about their diabetes and their baby's development; less mental burden, better sleep and a feeling of normality. During this phase of ongoing use, women noted that hybrid closed-loop therapy is not a panacea that they could "plug in and leave", optimal use involved collaboration with the system in terms of providing information it will not be able to identify itself especially surrounding carbohydrate intake and insulin requirements to account for this intake. Optimal use also involved collaboration with healthcare teams. Women noted that once they were used to the real-time nature and volume of insulin and glucose data shared by the system to healthcare teams, they found better, closer and more honest and trusting therapeutic relationships developed leading to better feedback and more personalised advice and care.

Table 3.5 Women's lived experience of type 1 diabetes pregnancy and hybrid closed-loop therapy
(adapted from Lawton et al 2023) (143)

Themes / Subthemes	Participant Quotations
Previous experiences of pregnancy with type 1 diabetes (prior to hybrid closed-loop)	
Physically, mentally and emotionally demanding	**1. Constant hard work and mental burden** [Managing diabetes in pregnancy is] "such hard work. it's so intense" (010), "tiring and draining" (005), "very stressful" (013) and "it kind of deprived me also of enjoying it [pregnancy]" (002). "It was constantly at the forefront of my mind over what to do… On the injections you're thinking: right, okay what ratio am I on? What's my carbs? What's my calculation to be? And then what's my correction dose on top of that… Because one day you could be on one ratio, the next day you could be on something else." (019) **2. Constant glucose monitoring and adjustment of insulin** Needing to "constantly prick my finger, constantly correct" (007) or "constantly chang[e] my basal rates, it was relentless" (005) **3. Becoming obsessed about monitoring and over-correcting** "I've been using a lot of temporary basals, and if anything I was doing overcorrection sometimes. So I was finding I was, you know, a bit- I'd be hypo and then sort it out, and then I'd go- get a massive rebound high... So I was getting a lot of peaks and troughs, and I was finding that, obviously with hypos I was eating more. So then that was making me feel worse." (022) **4. Use of nocturnal CGM alarms and fear of hypoglycaemia** "The hardest thing is at night I think, 'cause I've quite a fear of going low. So I'd set about three alarms overnight (laughs). You just end up not sleeping very well at all and I think that can kind of get you down." (010)
Limitations of tools available to them during previous pregnancies	"I didn't have a sensor, so I couldn't look back on what my sugars were doing through the night. So it was literally guessing." (005) This participant reflected if she had had CGM with alarms during a previous pregnancy: "I wouldn't have gone all night before I realised I was at 15 or 17 or something, and I could have taken a correction sooner." (015)

Experiences of the hybrid closed-loop system during pregnancy	
Initial development of confidence and trust in the hybrid closed-loop system	**1. Adjusting to the system** "It felt as though I was just constantly watching, making sure that it was doing its job, so I would be probably looking at it anywhere between- I would probably say six to ten times a day. I was constantly checking on it." (019) "I think by about 20 weeks I had about 82% time in target. Em, so I sort of saw that, I just thought like, this is, you know, I have to trust this. This is brilliant. So… the feeling of worry just kind of gradually wore off and I started to, yeah, just completely trust it was doing what it should do." (016) **2. Healthcare professionals' role in supporting this process** "I trusted it, because… I just… knew that obviously the ladies at the hospital were monitoring quite closely to make sure that it was correct, and so they could change it sort of from day to day if I needed to." (021) "It was easier to explain when you are using it, rather than as you set it up, you know, it's easy to say: oh this one means it's rising, this one means it's lowering, but it's not until I started using that that I realised I didn't actually fully understand the function and needed a bit more support." (014) "The training was very good, it was thorough, but you will be learning as you start to use it. I've messaged [names staff member] a couple of times, initially particularly when my sugars were going high, I was like: normally I'd give a correction here, I'm going to put the Boost function on: is that right?. Shall I use it for this amount of time or longer? - So it's just that clarification." (022) **3. Initial change in therapeutic relationship and getting used to having more information available to healthcare professionals** "It felt a bit Big Brother-ish at first, particularly when they would say: 'oh well you had, you know, X number of carbs after 7 pm last Wednesday or something." (015)

Benefits of hybrid closed-loop	**1. Less work, less worry… better glucose control** "Before… I was on it, like every couple of weeks I was having to keep changing all my basal rates and everything to try and keep up, whereas this just automatically does it, so it makes it much easier, it just takes a lot off you, like even the mental side of just constant viewing the data, it does all that for you." (010) "Without the system, I would have spent a lot more time and energy actually working to avoid it [hypoglycaemia]… I would have been actively working to avoid low ones as well, whereas with the system I just had to be aware and make sure I had treatments available if needed, you know, in a relatively low-key kind of way." (015) "It's definitely helped with the anxiety of running myself high to not go low, because I've got the alerts that tell me if it is gonna go low… And knowing that the closed loop will be picking up if you are starting to get low, that it's going to ease off." (007) "It's definitely took the worry away for me, 'cause I'm quite active in the day with my kids anyway, so if I'm dipping low, and I'm busy with the kids, I'm then alerted before anything goes wrong, because if I was to, God forbid, have a hypo and not be responsive with my children, it would be awful." (011) **2. Better sleep** "I think obviously being the closed-loop, it adjusts for you.in the background. 'cause I never really knew what my overnights were. Even with the Libre you have the Libre lows, my overnights were sort of all over the place. Whereas now I could have a steady night, and obviously sleep, and not have to worry too much about it." (021) **3. Enjoying more normality and being able to work for longer** "Honestly, it allowed me to work. I would never be able. to work at the job that I was doing [waitressing] at all, if I didn't have the machine." (002) "[Without the closed-loop] I wouldn't have gone out as much, and I wouldn't have done as much as what I done. I would have stopped work a lot more sooner than what I did... especially when you're self-employed, it does make a helluva lot of difference." (018)

Benefits of hybrid closed-loop	**4. Worrying less about their baby's development** "I didn't have that much fear for the pregnancy itself. And I think that's because of the closed-loop. So there are not that many concerns about the development of the- and the growth of the baby." (007)
Factors that facilitated diabetes self-management and better glycaemia	**1. Smartphone user interface helped feeling of normality and facilitated more proactive diabetes self-management** "Before… if my Libre said I was 12 [mmol/L] and I was in the playground with lots of other mums . and I knew I was going home in half an hour, then I wouldn't get my insulin pen out to give myself a correction. especially when you're pregnant, you don't wanna get your tummy out to (laughing) give yourself an injection. whereas you can do that now. So again, that's another factor that just means your time in target must be, yeah, just hugely better." (011) **2. Access to real-time insulin as well as glucose data** "Having the visualisation of the graph, knowing that it's not delivering any insulin at the minute. I think that's really helpful to know that it's already eased off, so I probably haven't got that much insulin in me that's going to send me lower. So you know, that one jelly baby is going to bring me back up to the level." (007) **3. Striking a balance of allowing the system to operate without interference and identifying when and how to assist the system** "The main thing I've struggled with is, like, obviously before when my levels went high I would just put a correction dose in. But I've still kind of struggled to know. when I should put a correction in or whether I should just let the phone do its own thing." (010) "Basically it [closed-loop] does know what it's doing, but you've got that manual override if you need to, so I think… you definitely still need to have an element of knowing what you're doing as well, knowing… the bits that the [closed-loop]. doesn't know, so like your physical exercise, the food that you've just eaten and things like that." (007) **4. Using "boost" and "ease off" features of the CamAPS FX hybrid closed-loop system** "Sometimes I use [Boost] where I think the algorithm hasn't been as generous as I think it needs it to be, because that's just the algorithm still learning, because I'm extremely insulin resistant." (022)

Factors that facilitated diabetes self-management and better glycaemia	"I used Ease-off a lot at work, especially if I could see that my blood sugar was sitting just slightly lower and I knew that maybe I wasn't having lunch for like another two hours or something, to then just try and prevent a hypo." (013) **5. Ongoing HCP support and real-time data link to healthcare professionals** "I've messaged (names trial staff) a couple of times, when I was sort of- initially particularly when my sugars were going high, I was like: normally I'd give a correction here. I'm gonna put the boost function on: is that right?" (022) "You can say: oh look, I'm having this problem. They'd have a quick look… it's like there and then, sort of, the help." (021)
Not a panacea: user collaboration required with hybrid closed-loop system to achieve optimal glycaemia	**1. Work still needed but not as much as without** "Maybe just anecdotally I've heard…it's like an artificial pancreas. And I think that sounds just wrong. And I think it gives false hope… because for me it's still a lot of your management." (011) "I don't have to worry about taking insulin, and I know that I'm actually getting insulin. The only time I need to worry about it, is putting the carbs in." (004) "Now the only thing I need to do is when I eat, put the carbs in, and then it's done, it's another weight off your shoulders" (010) **2. Considerations to help the system: carbohydrate counting, timing of boluses and dietary choices** "I still think… a lot of it is your own doing and the information you're putting in and when. Em, so your carb counting, the time before you're gonna eat." (017)

Better collaboration with healthcare teams	**1. Access to more detailed real-time data facilitates better feedback and personalised advice** "I think it's a good thing that you can basically do a live feed to them, because it means that they've got up-to-date data that they can look at and very quickly change something if it needs to be changed. They're not looking at the five days prior, and you're saying well, now, you're having troubles now. And they're going: well, we can't see that data, so we can only go by what happened three days ago." (019) . "It's nice that somebody else can look at this data. they can see the graph of what's going on, how it's happening, how much insulin I've had, how much background insulin I've had. So just because they've got all that data, they can then tell me the exact thing that I need to do, which then sorts it out straightaway." (020) … closer, more honest and trusting relationships with health care teams: "[It] allows me to communicate better, for them to understand better what I'm trying to say. And that communication, by being better, it builds trust. So I trust them more than if it was the opposite." (002) "They have a little bit more trust in me, because they see my data and they see it's going well, so they understand my independency (sic), while maybe before they were a little bit more hesitating in giving me that independence." (008)

Table 3.6 Patient-reported outcomes
(adapted from Lee et al 2023) (139)

Outcomes	Baseline ~12/40				Follow-up Phase ~34/40				Adjusted Treatment Difference
	Hybrid closed-loop		Standard care		Hybrid closed-loop		Standard care		(95% CI)
INSPIRE$^{\alpha}$	57	80 ± 10	NA	NA	34	82.9 ± 9.4	NA	NA	NA
EQ-5D$^{\beta}$	57	0.88 ± 0.15	59	0.89 ± 0.14	34	0.85 ± 0.16	44	0.76 ± 0.19	0.09 (0.02, 0.17)
Diabetes Distress Scale (DDS) total$^{\delta}$	57	2.1 ± 0.9	58	2.0 ± 0.8	34	1.5 ± 0.5	43	1.5 ± 0.4	-0.07 (-0.26, 0.11)
DDS Emotional	57	1.8 ± 0.8	58	1.7 ± 0.7	34	1.4 ± 0.5	43	1.4 ± 0.4	0.00 (-0.18, 0.19)
DDS Physician	57	2.1 ± 0.9	58	2.1 ± 0.7	34	1.5 ± 0.5	43	1.6 ± 0.4	-0.1 (-0.3, 0.1)
DDS Regimen	57	2.4 ± 1.0	58	2.4 ± 1.1	34	1.5 ± 0.5	43	1.8 ± 0.6	-0.3 (-0.5, 0.0)
DDS Interpersonal	57	1.9 ± 0.9	58	1.7 ± 0.8	34	1.6 ± 0.8	43	1.3 ± 0.6	0.1 (-0.2, 0.4)
HFSQ II – Worry$^{\phi}$	55	34 ± 12	58	32 ± 10	34	28 ± 10	43	29 ± 7	-0.9 (-4.8, 3.1)
PSQI$^{\lambda}$	42	9.2 ± 3.6	45	8.9 ± 3.1	28	11.3 ± 3.2	29	10.7 ± 3.4	1.8 (-0.2, 3.8)

Data are number of respondents in the left column and score presented as mean ± SD.
Difference is hybrid closed-loop – standard care adjusted for baseline value of the metric, insulin delivery modality, and site as a random effect.

α The INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) questionnaire (intervention group only). Higher scores indicate more positive experiences
β EQ-5D-5L Health-Related Quality of Life Questionnaire: total EQ-5D score, the maximum score of 1 indicates the best health state
δ Diabetes Distress Score – higher scores indicate more total, emotional, physician, treatment-related, and interpersonal diabetes distress.
ϕ Hypoglycaemia Fear Survey Questionnaire II (HFSQ II) (Worry scale only) – higher scores indicate higher fear of hypoglycaemia.
λ Pittsburgh Sleep Quality Index (PSQI) with higher scores indicating worse sleep quality.

Patient-reported outcomes

Out of 124 women included in the AiDAPT trial, up to 116 responded to baseline questionnaires and up to 78 competed the follow up questionnaires at 34-36 weeks' gestation (Table 3.6). There were no between-group differences in patient reported outcomes as assessed by the EQ-5D-5L Health-Related Quality of Life Questionnaire, the Diabetes Distress Score, the Hypoglycaemia Fear Survey (worry scale only) and Pittsburgh Sleep Quality Index (Table 3.6).

Healthcare professionals' views

Nineteen out of a possible twenty-two healthcare professionals who provided clinical care and support of women in the hybrid closed-loop intervention arm of the AiDAPT trial were interviewed between June 2021 and April 2022. They came from across eight sites and each had more than 6 months' experience supporting women using hybrid closed-loop therapy in pregnancy. Their characteristics are presented in Table 3.7. At the time of these interviews, the healthcare professionals included had supported approximately two-thirds of the women in the intervention arm of the AiDAPT trial.

Topics discussed by healthcare professionals through the qualitative interviews were categorised into two groups:

1. Their views on the hybrid closed-loop system (Table 3.8)
    - who, how and why women benefitted in pregnancy
    - factors that influence how well hybrid closed-loop therapy worked in pregnancy
    - what was required to optimise hybrid closed-loop use in pregnancy
    - Hopes, tips and concerns with respect to potential hybrid closed-loop therapy rollout (if found effective) with respect to individual women and patients
2. Potential challenges and possible solutions to rolling out hybrid closed-loop therapy in pregnancy (if found to be effective) with respect to services from a national healthcare service perspective (Table 3.9)

Table 3.7 Healthcare professionals' characteristics

(adapted from Lawton et al 2023 and Rankin et al 2023) (144,145)

Characteristic	N	%[α]
AiDAPT sites (n=8)		
Total number of interviewees	19	
Interviewees per site: range (mode)	1 - 4 (3)	
Role		
Diabetes consultants / doctors	11	57.9
Nurse consultants	2	10.5
Diabetes specialist nurses	4	21.1
Dietitian	1	5.3
Diabetes specialist midwife	1	5.3
Years of diabetes experience		
5-10 years	4	21.1
10-20 years	5	26.3
>20 years	10	52.6
Interviewees with previous experience supporting HCL users during trials or in routine care	12	63.2
Gender		
Female	16	84.2
Male	3	15.8
Age in years mean ± SD (range)	48.7 ± 7.1 (33 – 60)	

HCL = hybrid closed-loop

α Percentages may not add up to 100% due to rounding

When evaluating the role of hybrid closed-loop therapy, healthcare professionals often described it in comparison to standalone CGM (Table 3.8). In terms of hybrid closed-loop therapy, they described benefits similar to the women's lived experience. They found that the system was user friendly and that automation of the basal rates meant that women were able to work less on their diabetes self-management whilst still achieving the same if not better glycaemia. This lead to less worry, improved quality of life and better sleep. Some healthcare professionals described the ability of hybrid closed-loop therapy to compensate for suboptimal diabetes self-care behaviours: to some extent able they were to make up for missed or late boluses, and under- or over-estimated carbohydrate boluses. Overall however, they emphasised that hybrid closed-loop therapy required user input and work, although a balance was required to help the user trust the system and not overly interfere or duplicate the automation of the algorithm as well as engaging in responding to alarms and ensuring they were accurately managing their carbohydrate intake as much as possible (Table 3.8).

In terms of their role when women were transitioned onto hybrid closed-loop therapy, healthcare professionals described an intensive first 2-4 weeks of use. Support was required to teach women how to use the component devices: pump refills and set and sensor changes and then how to integrate the hybrid closed-loop functionality into their diabetes self-care: interpreting CGM patterns with respect to the automated basal insulin, focussing on carbohydrate counting and boluses, and thinking about how hypoglycaemia management may be affected. Ongoing support was also required with respect to supporting gestational changes to insulin-carbohydrate doses, insulin action and pre-bolus timings, and using further interactive features and settings of the algorithm including personal glucose target, "boost" and "ease off" (Table 3.8).

Through the study, healthcare professionals were able to explore their attitudes and beliefs regarding candidacy for hybrid closed-loop therapy. Most healthcare professionals interviewed described an inclusive approach to recruitment, partly due to the pressure of meeting trial recruitment targets. This meant including women who were perceived to potentially struggle with diabetes technology use:

"we didn't want to prejudge who would be suitable for it… we thought, 'we're gonna ask everybody who meet these [inclusion] criteria' rather than thinking 'oh well they're not good with technology, we better not'." (HCP-016)

Many were pleasantly surprised and pleased to give example of those who were predicted to struggle with optimal diabetes self-care behaviours (including accurate carbohydrate counting and pre-meal boluses) and still did well in terms of coping with the diabetes technologies and improving their overall glycaemia. This lead to healthcare professionals developing the view that all women should be offered hybrid closed-loop therapy. Many were also keen to emphasise this included those women who "did well" on their current diabetes therapies as their "hard work" should not be penalised by withholding hybrid closed-loop therapy from them under the belief that they "did not need the hybrid closed-loop therapy". These women would still benefit from the unburdening of intensive aspects of their diabetes self-care behaviours by the hybrid closed-loop system and were also deserving of less worry, improved quality of life and better sleep. There was also the recognition that these women may also need extra support for a different reason: managing expectations and helping them allow the system to unburden some of their diabetes self-care and to let it learn for longer term benefits to quality of life and wellbeing. Lastly, healthcare professionals also highlighted that cost should not be an issue as many areas of the NHS were already funding CGM and insulin pump therapy separately so the additional cost of the hybrid closed-loop system was minimal in comparison (Table 3.8).

Table 3.8 Healthcare professionals' views on hybrid closed-loop technology and its role in type 1 diabetes management in pregnancy (adapted from Lawton et al 2023 and Rankin et al 2023) (144,145)

HCL = hybrid closed-loop therapy, HCP = healthcare professional

Themes / Subthemes	Participant Quotations
Using CGM alone has benefits and effects on diabetes self-management	**Benefits of CGM** **1. Preventing hypos** "I think the CGM's made such a difference to people in preventing hypos… and that means that we can be a bit more aggressive with the insulin changes, because you're less worried about hypos, particularly in the first trimester that are a real concern." (HP-002) **2. More glycaemic information to base food and lifestyle choices and insulin dosing** "what CGM has, does, is it … means that women can understand the impacts of their food choices on their day-to-day glycaemia … And then the CGM gives us much information around the impact of the food and lifestyle choices on glycaemia, that helps us to customise the insulin doses that you can to the particular person in front of you." (HP-014) **3. More glycaemic information overnight** "it enables, well, it should enable, the visualisation of results in a way that allows them to make changes themselves … the simple things like being able to see what's happening overnight. So you're able to change your insulin levels overnight … whereas before, we, we couldn't do that. Or it was much more difficult to do that. You were basing your overnight values on what was happening in the morning, and that was often a crude – so it improves the, the granularity of the things, the decisions that we're making." (HP-006) **However, increased glucose data can worsen anxiety and distress** "well, 'cause the targets they're aiming for are so tight, it's really hard – or impossible – to achieve what we're aiming at. I think being pregnant's really difficult anyway, 'cause you feel this sort of sense of responsibility towards your unborn child … I think sometimes the CGM is a kind a of double-edged sword, cause suddenly you're aware of all your blood sugars, and every time your blood sugar's 12, you think, 'Am I gonna harm my baby?'" (HP-016)

Added benefits and role of the hybrid closed-loop therapy in diabetes self-management	**1. Less work…** "it seems to just take away the complexities of the hour-to-hour glucose management that we, that often women struggle with … the closed-loop takes some of that pressure away." (HP-007) "what they're having to do is so much less, as well … it's less work for them definitely, while achieving better control." (HP-017) **… by adjusting automatically to gestational changes in diabetes self-management and achieving pregnancy glycaemic targets** "I think it's really great in pregnancy, because it fulfils that really unique role, where things change on a day-to-day, or week-to-week basis … having a little bit taken over and automated, so the women don't have to think about it, and worry about it, makes a huge difference… [and] the majority of women do really, really well … they're over 70% time-in-range, and they love it, because to achieve that, they haven't had to work as hard." (HP-018) **2. Leads to improved quality of life, less worry and better sleep** "I think they're totally transformational for women, not just in terms of glucose control, but in terms of quality of life." (HP-010) "it does improve … patients' quality of life in pregnancy, it's one less thing for them to have to worry about. Well, they still worry about it, but not as intently." (HP-019) "one of the women said to us, in clinic … '(I) wake up in the morning and the first thing I think about is not diabetes, and this has been the first time in my life that I've been able to do that'." (HP-003) **3. HCL does also compensate (to some extent) for some suboptimal diabetes self-care behaviours** "We had one of our very early participants and I think she probably didn't use it that well, and I think possibly had she not had the closed-loop, she would have [had] a very different outcome. Because it did pick up all the rubbish of her not correcting properly or not injecting, not carb counting, erratic eating patterns. And I think the closed-loop really softened that blow." (HP-019)

Added benefits and role of the hybrid closed-loop therapy in diabetes self-management	**4. Overall still requires work and user input** "you still have to do stuff to really get the … extraordinary control that is possible … it's definitely not just plug it in and leave it… it's the Aston Martin of the pump world, but you still need someone to drive it." (HP-004) "it's not a fix (for) everything … this doesn't mean that you're not longer driving your diabetes. It's a case of being able to … take your eye off the ball, just a little bit. But … it doesn't take care of everything … you haven't actually got an artificial pancreas … it's only as good as the person who's using (it)." (HP-005)
Factors that affect how well the hybrid closed-loop system can function	**1. Lack of engagement to the system: not responding to alarms, missed, inaccurate or mistimed boluses** "where it doesn't work quite so well is where I suppose there's lack of engagement. So if you're not bolusing at the correct time, or you ignore your alarms … it can't do everything … And then there's the patient who doesn't trust the system and is micro-managing … they'll start boosting and everything when perhaps it needs you to let the pump do its job. But they … just can't let go … So there's sort of two types where it's not working well." (HP-015) "the biggest limitation to using it (the HCL) … will be mis-timed, or not given, or mis-calculated boluses. The closed-loop will tend to mop that up a little bit, but never as much as people think." (HP-014) **2. Not trusting the system and wanting to be more actively involved with controlling glycaemia and influence the HCL more** "Some women … they're so used to doing everything themselves … (that) they aren't able to give up that part." (HP-018) "We did have one woman who was probably using 'Boost' too often… which just didn't really allow the algorithm to learn very well, because she was boosting all the time. So we discouraged it, and she seemed to settle down." (HP-007) "we did have one participant who withdrew … because she couldn't tinker with it essentially. Because she wanted to be able to influence it … She just felt uncomfortable … She liked to be able to give extra boluses, and adjust more things than she could." (HP-003)

Collaboration: a condition of maximum benefit	**Maximum benefit relies upon three-way collaboration between the healthcare team, the women and HCL** **1. Ongoing healthcare support…** "if we're going to look at offering these systems more widely, (we) would have to offer the package … it isn't just, you know, plug in and play. You don't just say, 'Here you go, here's a pump and the app, and bye-bye'. You have to give them that support." (HP-010) **2. … to build trust in the system and experience into when to step in and work with it** "I think probably the optimal psychological approach is to trust the system enough. So it's being a bit relaxed about the diabetes, but not too relaxed. And that's a really difficult balance. So not interfering with it too much, letting it get on and do its thing… but still being very engaged with your diabetes to make sure you're giving the boluses and all those kind of things." (HP-003) "When people aren't too controlling … the better they do, because the pump can do its thing, the algorithm can do its thing. But yeah, that's quite hard … when they're pregnant." (HP-001) **3. … to focus on things they can do to optimise conditions for HCL to perform optimally: dietary choices, carbohydrate counting and pre-meal bolus timings** "I try to stress to them that … to get the most out of using closed-loop, it's almost like when … they first started taking insulin and they were very careful about the timings of it, and careful about their eating, that the closed-loop will work best under those sort of scenarios." (HP-014) **4. … to understand role of interactive features such as boost and ease off, how they work and how they affect the HCL** "… making sure that if they're using the 'Ease-off', that they're using it for a good amount of time, and checking what their basal is doing before they switch it on – 'cause if it's hardly giving any insulin anyway, (there)'s not really much point!" (HP-002)

Collaboration: a condition of maximum benefit	"The issue … is the knowing when to use the 'Boost' and the 'Ease-off' … sometimes that's an issue. And sometimes women are just boosting when perhaps they … should be looking at their bolus doses, rather than just giving a dose and then giving a boost." (HP-009)
Predicting candidacy for the provision of hybrid closed-loop technology in routine care	**1. HCPs felt that all women who used HCL in the study (except those who withdrew) experienced benefits** "the overwhelming theme is that everyone does better with it, than without. Like definitely, a hundred per cent." (HP-005) **2. … even those who were predicted to struggle with management supportive of optimal HCL use** "there was one woman in particular who was pretty hopeless at looking after diabetes outside of pregnancy and has done very, very well… We thought, 'Should we be putting her in the trial?' We did, because she met the criteria. And we were slightly nervous, thinking, 'Well, this could be a disaster, maybe she'll just get frustrated and pull out of the trial'... But no, she didn't." (HP-009) "I'm surprised how quickly a couple of people that went on it – they just took off with it. Like one woman who's a bit flaky, but ever so nice, she went on it. And we … every time we speak, she says, 'Oh fine, brilliant'. She just took to it straightaway, and that, that was it." (HP-016) "one of our patients … it all looked pretty haphazard, (and) we had to keep reminding ourselves that before she went on to closed-loop she was 40% in target. And when she went on the closed-loop, she was 60% in target. So … significant improvement." (HP-009)
Hybrid closed-loop hopes, tips and concerns for use of hybrid closed-loop therapy in routine care	**1. Hopes for the study – to provide evidence for universal use of HCL in pregnancy** "I'm really hopeful they'll show benefit and … we can use it with loads more pregnant women with type 1. We can offer it … that's what I would like, you know, like we can with Dexcom. We can offer it to everyone with type 1. I'd love to be able to offer this as well." (HP-001)

Hybrid closed-loop hopes, tips and concerns for use of hybrid closed-loop therapy in routine care	**2. Including those who work hard on their diabetes self-management and achieve optimal glycaemia in order to reduce their self-care burden** "Some people have very good control because they're doing an amazing job of managing their sugars, and actually their life could be easier if they had this system … you know, some people do get up at ridiculous o'clock to give themselves extra insulin, et cetera, et cetera, and maintain great control that way. And a system that would support that, without their… intervention, would make their life much easier." (HP-015) "One would hope it would be any type 1 patient would be entitled to use a closed-loop system for the duration of their pregnancy. I would hope they wouldn't put a "too good control" limiting factor on it, but they might … One would hope it would be equal access for everyone." (HP-015) **3. Concerns HCL lead to frustration and anxiety to those whose self-management behaviours have evolved to "do everything" themselves even if temporarily or initially at transition** "People who have got to the point of managing their own diabetes by tinkering with everything themselves, I do think that the closed-loop, because it's part automated, doesn't do as well for them … They essentially have been running themselves like an insulin pump, without having a pump." (HP-007) **4. May widen access of insulin pumps to individuals that healthcare may not manage a standalone pump as HCL system automates some of the tasks** "it's certainly easier having a woman on closed-loop, than it is having a woman on a pump separately, because … you have to know a lot more about pumps … to make them work, than you do about a pump used in a closed-loop system. So, if people are worried about insulin pumps, then actually closed-loop is easier, and safer, than a pump used in a stand-alone system." (HP-003) **5. Cost should not be an issue** Where the NHS was already funding CGM and pump technology, the additional cost of providing access to a HCL would be minimal, and, indeed, it would be "almost criminal" (HP-014) not to meet this.

The second main category included in healthcare professional interviews explored their views on current infrastructure and services involved in diabetes care during pregnancy and what would be needed and could help facilitate a successful national rollout and robust ongoing provision of hybrid closed-loop therapy in pregnancy. Healthcare professionals acknowledged that currently maternity and the NHS as a whole is already a stretched workforce and that existing staff are limited in both time and number, and skills and expertise take time to develop. They emphasised the need to staff these specialist services robustly and with reserve to account for leave and sickness.

Healthcare professionals also highlighted scenarios where ensuring equitable access to hybrid closed-loop therapy for patients across the country may be more challenging. They felt that smaller sites with smaller populations of type 1 diabetes patients may need more upskilling of the staff existing knowledge base. Smaller numbers of patients may mean that it may take longer and require more external support to embed and maintain healthcare knowledge and skills especially if long gaps between caring for women becoming pregnant. Geographical challenges could exacerbate these disparities in upskilling, maintenance of expertise and felt that this needs to be focussed on to avoid disparities in access for the women (Table 3.9).

Healthcare professionals also highlighted the fact that diabetes in pregnancy care is not just delivered by specialist diabetes and obstetric teams. They emphasised the upskilling of the wider body of hospital staff including Accident and Emergency, general maternity including community midwifery and delivery staff – anyone who may provide care for these women acutely or during obstetric admissions. Lastly healthcare professionals acknowledged that CamAPS FX is not the only hybrid closed-loop system commercially available. If other systems were found to be of clinical benefit during pregnancy and to support patient choice, multiple systems would increase the complexity and volume of knowledge required for staff. One solution raised by some interviewees was to restrict the numbers of hybrid closed-loop systems offered, if only temporarily or initially (Table 3.9).

Healthcare professionals were then asked for possible solutions or ways these challenges could be addressed. Many found the resources made available to them via the study valuable and would want nationally online resources of a similar nature freely available: recordings of webinars and checklists that would be available to healthcare professionals to upskill at a time of their choosing as well as masterclass meetings and workshops. They also described

the pathway of having the AiDAPT trial research education training the first few participants alongside the local team before stepping back to assist remotely when local teams felt confident to do so. Healthcare professionals felt this could be one solution to rapidly upskill local staff. An alternative that was suggested was to have industry representatives from insulin pump companies provide this initial training for all patients with local teams providing ongoing support, as is the case in many areas of the NHS with standalone insulin pump use. A third suggestion was for training and / or hybrid closed-loop provision to be centralised with larger experienced teams supporting the women if only temporarily to speed up rollout and initial access (Table 3.9).

For ongoing support to healthcare professionals, many interviewees emphasised the importance of a technical support telephone service that was available 24/7. This, they felt should be provided by manufacturers, as is already available for CGM systems:

"You can't just bung the technology out there and expect individual sites to be able to answer all the questions. You're providing a commercial product… So, the manufacturer has to provide that help."(HP-007)

Lastly, interviewees suggested options for ensuring maintenance of expertise in the form of peer support. This could be via individual mentor and peer pairs locally or regionally; wider regional hub and spoke multidisciplinary teams (MDT), where experience is shared and difficult cases are discussed: or an online portal where CGM and insulin reports could be posted and someone with expertise could call and give feedback to support decision making (Table 3.9).

Overall, healthcare professionals felt that from their experience of hybrid closed-loop therapy in pregnancy during the AiDAPT trial, widespread uptake and use of hybrid closed-loop would help women improve their glycaemia and self-management and this would alleviate burden on diabetes in pregnancy services overall. Thus, initial investment in overcoming challenges to development of hybrid closed-loop services, upskilling of staff and ensuring equity across the country would be worth it to the service in the long-run (Table 3.9).

Table 3.9 Healthcare professionals' views on potential challenges and possible solutions to national healthcare service level rollout and provision of hybrid closed-loop therapy in pregnancy

(adapted from Lawton et al 2023 and Rankin et al 2023) (144,145)HCL = hybrid closed-loop

Themes / Subthemes	Participant quotations
Challenges to developing and maintaining robust service provision to support hybrid closed-loop therapy in pregnancy	**1. Limited time and existing staffing and skills take time to develop** "you really only get the sense of the data . once you do it lots" (HP-013) "We have a very stretched workforce and this is not top of the list of priorities. And I don't think they see it as necessarily for them [upskilling]… because they don't even have the capacity to put that effort in... If I'm worried about doing it [in a large centre], imagine what smaller places… would be like... who've perhaps even got less support or are less interested." (HP-011) **2. Ensuring sufficient reserve in service provision** "One of the challenges is making sure that enough members of the team are competent to manage it and for it not to become so specialised that only two clinicians out of the team of eight, actually know what they're doing… that we don't limit that to so few consultants, that if somebody's on holiday for a week, there's nobody who can help. I think that's quite a big challenge." (HP-010) **3. Smaller sites with smaller population of type 1 diabetes patients** - **may need more upskilling** "I think if you have pump knowledge and CGM knowledge the closed-loop is very straightforward. [However,] pump is still not universal and so depending on the centre, maybe some of the bigger centres have 30, 40% of people on pumps, some centres have only got 10% on pumps, so pump knowledge is very variable." (HP-009) - **may need more support to embed and maintain skills** "you have two or three months break [gap], and you go: 'oh my God. What was it, that thing we said we must remember for this time?'" (HP004).

Challenges to developing and maintaining robust service provision to support hybrid closed-loop therapy in pregnancy	**4. Geographical challenges could exacerbate disparities in service provision** "Some areas of the country, patients aren't going to be able to travel. maybe in, I don't know, the Highlands of Scotland or… some places in Cornwall… are we saying that those people won't be able to access it… just because they live round the corner from (names experienced hospital) that shouldn't be the reason for access." (HP-013) **5. Need to upskill the wider body of hospital staff (Accident and Emergency, Maternity Assessment and Delivery units)** For when patients are presenting acutely (e.g. in diabetic ketoacidosis) or admitted "wider healthcare professionals aren't doing things they shouldn't be doing" (HP-015) and there are pathways for specialist support to these healthcare professionals during and out of hours. **6. Multiple systems increases complexity and volume of knowledge required** [There are several HCL systems] ''which are all slightly different'' (HP-016) "The average maternity clinic will have 20 women with type 1 a year. So, if they were going to put ten women on systems and they had access to three or four different systems, it's going to be hard." (HP-014) - **One interviewee suggested limiting the number of HCL systems offered if in a small site with fewer type 1 diabetes patients** "If you've only got, let's say ten women with type 1 coming through your service, having to learn three different systems is- is really hard. So being able to say, yes, we can offer closed loop, but it will be this system, is a possibility." (HP-003)

Suggestions to support training of healthcare professionals in the event of hybrid closed-loop rollout	**1. Training resources like online videos of webinars, checklists and masterclass meetings or workshops** "Have really clear checklists about what needs to be done… how you link everything together, what the patient must do, and what you must sign off [with] the patient. so they look at the videos, they know what to do." (HP-013) [Emphasis on providing succinct checklists to limit] ''having to read a hundred and fifty-page user guide'' (HP003) **2. Training infrastructure to support clinical teams to develop and consolidate local HCL expertise** **i) Expert to help guide initial training** "She [research educator] did the first patient and we were both there… the second one we did… but [research educator] was watching virtually. And then after that . [research educator] was there if we got stuck. So that was brilliant… That's a much better way of learning, certainly for me." (HP-003) **ii) Expert could be from industry to help reduce burden on NHS** "I think this is similar to going onto general pumps… getting people, like reps from the company. So, like pump starts for Dana, Medtronic… and they train the women… basically like [research educator], who works for CamAPS as opposed to working for the NHS." (HP-018) **iii) Alternatively training and/or HCL provision could be centralised** A few HCPs suggested that training and clinical support could be "led from a central point" (HP-006) or "centres that are a bit more experienced supporting local teams . at least until [local] centres are more familiar with using the technologies" (HP-014). **3. Importance of technical telephone support for healthcare professionals** [that is] "available on hand, 24/7" (HP-001) "You do kind of need that expert support kind of on-hand, to be able to call somebody and say: right, this is happening… tricky things like: the app's not working, the transmitter's failed, you know, I've tried this, this and this, what next?" (HP-002)

Suggestions to support training of healthcare professionals in the event of hybrid closed-loop rollout	**i) This could be provided by industry as already the case with some CGM systems** "I suppose like any commercial product like Libre or Dexcom, you're going to have to have a national 24-h helpdesk, aren't you?... It's a bit like you know, if you produce an insulin pump… or provide Dexcom, you have to have a helpline, an easy, accessible, functional, user-friendly helpline. You can't just bung the technology out there and expect individual sites to be able to answer all the questions. You're providing a commercial product… So, the manufacturer has to provide that help." (HP-007) **4. Having infrastructure or pathway to share experience between sites and provide support when first starting out and ongoing for difficult cases and ensure parity across regions seek support from experienced individuals or team locally or regionally** "[What's] been really helpful on occasion is, where I've been able to talk to [central trial staff] about, carb ratios, and when to strengthen them and when to weaken them, and use ease-off and boost… sometimes it can get a bit hard to know which bit of the algorithm is working when." (HP-004) **i) Could be an individual mentor and peer pairing locally or regionally** "I think just having a mentor until you've got going… someone to ring up. who you share downloads with and say: this is what I did… What do you think? You know, I think that would be valuable." (HP-015) **ii) Could be a wider regional hub and spoke MDT set up** "Maybe having wider support meetings if you like… a Type 1 pregnancy technology MDT [multidisciplinary team meeting], where we discuss just a couple of cases every couple of weeks, with the wider team in more detail, so that we upskill if you like, other people in the team, who are not doing technology so much… and if you could get that between centres, being able to share that experience is really important." (HP-003) "to hear about other people's experiences of what had gone wrong and what had gone well" [was really helpful] (HP-002) **iii) Format could involve an online portal** "you could drop the image of what you're unsure about, and then somebody who has expertise could perhaps either call you, if that's necessary, or could give feedback based on what they can see." (HP-006)

Use of hybrid closed-loop therapy is worth the initial investment in terms of developing services and training of each individual	**Widespread uptake and use of HCL in pregnancy will in the long-term reduce the amount of time and overall support required by the type 1 diabetes pregnancy population** [It is] “a lot less onerous” (HP-004) [to support women using HCL] “if women are getting [more] time in range. through the technology doing it, we’re probably going to have less input into micromanaging them” (HP-007) [Others observed that women using HCL experienced fewer episodes of hypoglycaemia] ‘‘later support is hopefully less burdensome, if indeed there are fewer hypos and fewer overnight hypos’’ (HP-012). “if we could put the type 1s on the automatic pump, that would do at least some of the work for us. It’s the CGM data that’s the issue, looking at the CGM data. And that’s why closed-loop is good because you’re only looking at . the post meal bit. Whereas when you’re looking at the CGM data for open loop and MDI you have to look at everything.” (HP-009) “what I need to know, across a clinic or a population base level. So it’ll instantly highlight women who are above or below target, anyone who’s having a ton of alarms, anything that’s kind of out of the ordinary.” (HP-014) “It does give you just a general brief overview. you can cast your eyes over and be like: ‘oh, they’re not doing too badly, or the time in range isn’t too bad. That’s someone I don’t need to focus on so much, whereas it might highlight someone else that you do need to focus on.” (HP-019)

3.6 Discussion

Both women and healthcare professionals described through qualitative interview, many glycaemic and quality-of-life benefits of using hybrid closed-loop therapy in pregnancy. However, both groups also acknowledged that optimal hybrid closed-loop use involves three-party collaboration between the women, the technology and the healthcare team. When first starting hybrid closed-loop therapy, both women and healthcare professionals describe an intensive first few weeks whilst the women are learning to use the system and integrate its function into their diabetes self-care. It is during this time that comprehensive, accessible and compassionate psychosocial as well as clinical support from healthcare professionals can help women rapidly gain confidence and expertise in using hybrid closed-loop therapy to manage their diabetes and alleviate some of their diabetes self-care burden and pregnancy-related anxiety.

In this study, though women did experience some initial anxiety when transitioning onto hybrid closed-loop therapy, they did not report the same level of negative psychosocial and lifestyle effects, (including technology glitches, the impact of safety alarms, feeling overwhelmed by glycaemic data, increase needs to maintain use of hybrid closed-loop therapy, and worry of dependency on the system and deskilling of diabetes self-management) as reported in previous hybrid closed-loop studies (136,137). It may be that increasing use and familiarity of diabetes technology in routine care have adjusted expectations and normalised some of what would have previously been unusual experiences.

Women and healthcare professionals described positive outcomes of hybrid closed-loop therapy: improved quality of life; less worry especially around the pregnancy and baby's development; better sleep; a feeling of normality, and the ability to build more trusting and honest therapeutic relationships. Part of this development of improved healthcare – patient therapeutic relationships were driven from the woman: they were less worried about being criticised for suboptimal glycaemia. From the healthcare professionals' perspective, as all the glycaemic and insulin data were accessible, they could more readily identify challenges women were experiencing and address them. Women who were initially hesitant about the volume of data being shared with their healthcare teams, were reassured as they experienced better therapeutic relationships and that the increased access to their diabetes data was helpful and not being abused.

Women were overall keen to maintain active roles in their diabetes self-management and appreciated the support and training to do so. This included engagement with and desire to master interactive functions that influence the automated algorithm: boost and ease off. This is in contrast to other user groups who were more likely to welcome the unburdening and delegation of diabetes self-management to the system (141,142,150). This is understandable given the strong feelings of responsibility over the development and wellbeing of their pregnancy and baby and the tighter pregnancy glycaemic targets (31,118,125,127). This was also recognised by healthcare professionals who emphasised the importance of being able to develop and maintain services that were able to provide specialist pregnancy-specific expertise, training and support for these women.

It is notable that there were no differences in the patient-reported outcomes between those using hybrid closed-loop therapy and those in the standard care arm. This is in keeping with previous hybrid closed-loop therapy in pregnancy studies (87,136). Whilst these questionnaires are validated, they are not tailored to capture the complexities of diabetes in pregnancy and the immediate postnatal period (151). Qualitative interviews provide rich and comprehensive data but they are also costly in financial terms (given grant funding limitations), time intensive and require specialist expertise. More recently, there has been work into developing patient-reported outcomes specifically for pregnancy- and postnatal populations. This will hopefully widen the inclusion of women's lived experiences in future diabetes pregnancy research studies (151–153).

The AiDAPT trial healthcare professionals developed the viewpoint that all women should be offered hybrid closed-loop therapy. Their preconceived ideas about who may or may not benefit from the study were challenged and they found that women of different levels of engagement with the system and their diabetes self-care, all benefited from hybrid closed-loop use. Therefore in the event of national rollout of hybrid closed-loop therapy in pregnancy, they were keen to ensure that women who were "doing well" and worked hard on their diabetes self-care on existing insulin therapies were not exempt from hybrid closed-loop provision, as they would benefit from the quality of life improvements including an unburdening of some of their diabetes self-management.

Healthcare professionals were also positive about the impact of hybrid closed-loop therapy on overall diabetes in pregnancy management. They felt that despite the challenges to ensuring

robust and equitable rollout across the country, it was worth the initial effort to improve overall care of the women and reduce burden on diabetes in pregnancy services.

Strengths and limitations

To the best of our knowledge, the women's lived experience study is the first study to describe women's lived experiences of using a commercially available hybrid closed-loop system from early pregnancy to delivery. The use of qualitative interviews in addition to questionnaires provided a richness and detail to more accurately reflect women's experiences. Despite not interviewing the standard care arm women, women were included who could compare previous experiences of pregnancy without hybrid closed-loop therapy. Women were intentionally included to ensure views from a wide range of socio-economic backgrounds. A limitation is that due to the timing of interviews, it was not possible to explore experiences of use of hybrid closed-loop therapy during hospital admission for labour and delivery.

The healthcare professionals' study is the most detailed study to report healthcare professionals' experiences of supporting hybrid closed-loop use in pregnancy. The experienced qualitative interview team built a good rapport with interviewees in order to collect truthful and accurate insights relevant to clinical practice. Views and opinions were shared in the context of a confidential research interview and so there are limitations with presenting short quotations out of their full context of the complete one- to two-hour interview. It is also to be noted that by delivering a diabetes technology study, interviewees may be technology enthusiasts which will impact their views and enthusiasm for widespread hybrid closed-loop use. When considering national rollout in a health service, this study was performed in the context of the UK NHS system so further work with local stakeholders would be beneficial when applying to other healthcare systems.

Conclusions

Both women and healthcare professionals were enthusiastic about hybrid closed-loop use in pregnancy describing many glycaemic and quality-of-life benefits. For maximum benefit, both groups acknowledged their respective roles in a three-way collaboration where the technology was only one of the three pillars. The detail to which interviewers explored challenges and highlighted healthcare professionals' emphasis on the importance of developing robust, sustainable services across the hospital, in order to properly initiate,

support and maintain hybrid closed-loop use in pregnancy will hopefully assist in a successful national rollout.

Chapter 4: Postpartum use of hybrid closed-loop therapy, an AiDAPT extension study

4.1 Chapter Introduction

Chapters 2 and 3 outline the main biomedical and psychosocial analyses from the AiDAPT (**A**utomated **I**nsulin **D**elivery **A**mong **P**regnant women with **T**ype 1 diabetes) study examining hybrid closed-loop therapy in type 1 diabetes pregnancy. This chapter presents the postpartum extension study examining the continued use of the CamAPS FX hybrid closed-loop system in the first six months after pregnancy.

4.2 Chapter Summary

Background: Clinical guidelines in the UK and elsewhere do not specifically address hybrid closed-loop use in the postpartum period when the demands of caring for a newborn are paramount. Our aim was to evaluate the safety and efficacy of hybrid closed-loop use during the first six months postpartum.

Methods: In an extension to a multicentre, randomised controlled trial, pregnant women with type 1 diabetes at nine UK sites were followed for six months postpartum. Eligible participants continued their randomly assigned treatment: standard insulin therapy with continuous glucose monitoring (CGM) or hybrid closed-loop therapy (CamAPS FX system). They were randomised on a 1:1 basis with stratification by clinical site using randomly permuted blocks. Primary outcome was the between-group difference in percentage time spent in target range; 3.9–10.0mmol/L, examined during 0 to <3 months, 3 to 6 months, and over 6 months postpartum.

Results: 57 participants (mean ± SD) age 31 ± 4years and early pregnancy HbA1c 59.4 ± 10.5mmol/mol were included. Mean time with glucose levels within target range was higher; 72 ± 12% vs. 54 ± 17% (adjusted treatment difference, 15% [95% CI, 7-22]) over six months postpartum. Results for hyperglycaemia (>10.0mmol/L) and mean CGM glucose also favoured hybrid closed-loop therapy (-14% [-23%, -6%] and -1.3mmol/L [-2.3, -0.3], respectively). Hypoglycaemia rates were low with no between-group differences (2.4% vs 2.6%). There were no treatment effect changes depending on postpartum period (0-<3 vs 3-6 months) and no unanticipated safety problems.

Conclusions: Hybrid closed-loop users maintained 70% time in range during the first six months postpartum, supporting continued use of hybrid closed-loop therapy into the postpartum period over standard insulin therapy.

4.3 Background

The daily management of glucose levels in type 1 diabetes is challenging. Maintaining safe maternal glycaemia in the postpartum period is complicated by the profound physiological changes that occur after delivery and lifestyle changes associated with caring for a newborn. Following delivery of the placenta, insulin sensitivity dramatically increases, however, there is considerable inter-individual variability with some individuals requiring minimal exogenous insulin in the initial 12-24hrs (154,155). During the months following delivery, changing maternal hormones, unpredictable daily routine, and variable maternal and infant feeding patterns further complicate diabetes management and insulin dose adjustment (156,155,157,158). Sleep deprivation and exhaustion exacerbate the mental burden of glycaemic self-management alongside caring for a newborn – both of which demand constant attention. These postnatal diabetes challenges are further compounded by a gap in care as women transition from intensive antenatal support (2 - 4 weekly appointments) to general diabetes services (2 – 4 appointments per year) with many describing "being lost" and "not knowing who to turn to when they had trouble or needed support" (31).

4.3.1 Impact of infant feeding on maternal glycaemia

The WHO (World Health Organisation) categorises infant feeding into the following groups:

i) *Exclusive breastfeeding:*
the infant takes only breast milk and no additional food, water, or other fluids with the exception of medicines and vitamin or mineral drops

ii) *Predominantly breastfeeding:*
in addition to breast milk and above, other liquids such as water, water-based drinks, fruit juice may have been given to the infant

iii) *Artificial feeding:*
the infant is given breast milk substitutes, e.g. formula and no breast milk at all

iv) *Mixed feeding:*
the infant is given a combination of breast milk and breast milk substitutes

The WHO recommends exclusive breastfeeding over the first six months with complementary feeding, i.e. the introduction of complementary foods to meet the evolving nutritional requirements, thereafter (159). There are benefits of breastfeeding for both mother and baby (160). For the mother, this includes a reduction in future rates of breast and ovarian

cancers, obesity and cardiovascular disease and for the baby, protection from infection and reduction in childhood obesity and type 1 and type 2 diabetes, including in the context of maternal pre-gestational diabetes (160–165).

Due to the high calorie content of milk and the energy required in its production, lactogenesis can have an impact on maternal glycaemia. Maternal calorie requirements are estimated to increase by 400 calories a day when exclusively breastfeeding. Owing to this, both women and healthcare professionals have concerns regarding hypoglycaemia associated with breastfeeding, especially at night (151,166).

Studies evaluating the effect of breastfeeding in the postpartum period among women with type 1 diabetes have small sample sizes with limited follow up: one extended to six months postpartum and a further study extended to twelve months postpartum They are conflicting in terms of insulin doses and rates of hypoglycaemia between breastfeeding and artificial feeding, though this may be due to heterogeneity of the studies with variable adjustment for maternal confounders (e.g. dietary intake, insulin regimen, physical activity) and the variation in assessment of insulin doses (units/day vs. units/kg/day). Eleven studies examined insulin doses with respect to infant feeding during the postpartum period in women with type 1 diabetes (Table 4.1) (167–177).

Nine compared insulin doses between women who exclusively breastfed to those who fed their babies with breastmilk substitutes (with or without breastmilk: mixed or artificial feeding) (167–171,173–176). Three studies found that women who breastfed had lower insulin doses, with six finding no differences between the two groups. Seven studies assessed post and pre-pregnancy insulin doses in breastfeeding women with five demonstrating lower postpartum insulin doses and two finding no difference (167–170,172,174,175). These seven studies compared pre- and post-pregnancy insulin doses for non-exclusively breastfeeding women, with three studies reporting decreased postpartum insulin doses and four finding no change.

Table 4.1 Studies evaluating insulin requirements and rates of hypoglycaemia in the postpartum period

	Participants	**Postpartum follow up (weeks)**	**Insulin doses breastfeeding (BF) vs artificial feeding (AF)**	**Insulin doses postpartum BF vs. pre-pregnancy**	**Insulin doses postpartum AF vs. pre-pregnancy**	**Hypoglycaemia**
Fresa et al 2024 (177)	N=6 6 BF, 1 AF	4	N/A	N/A	N/A	TBR <3.0mmol/L BF: 0-3% | AF 2%
Skajaa et al 2023 (176)	N=66 32 BF, 34 AF (at 24/52)	4, 12, 24 and 52	↔	N/A	N/A	N/A
Ringholm et al 2019 (175)	N=33 26 BF, 7 AF (32 controls)	4, 8 and 24	BF < AF	Lower postpartum 4/52 (-18%) 8/52 (-14%) 24/52 (-4%)	Lower postpartum	No difference between BF, AF and control
Achong et al 2016 (174)	N=16 8 BF, 8 AF (6 controls)	8-16	↔	↔	↔	No difference between BF and AF but both reduced compared to control overnight
Roeder et al 2016 (173)	N=44 35 BF, 9 AF / mixed	?	↔ (assessed by TDD)	N/A	N/A	N/A
Inkster et al 2015 (172)	N=6 4 BF, 2 AF / mixed	1-4	N/A	↔ (Basal doses only)	↔ (Basal doses only)	No severe hypoglycaemia events
Riviello et al 2009 (171)	N=18 12 BF, 6 AF	1-8	BF < AF	N/A	N/A	More hypos in BF than AF over 2/52
Stage et al 2006 (170)	N=102 55 BF, (14 mixed), 33 AF	16	↔ (assessed by TDD)	Lower postpartum @ 4 months	↔ at 4 months	No difference between BF and AF at 4 months postpartum
Saez-de-Illbarra et al 2003 (169)	N=36 24 BF, 12 AF	1, 4, 8	↔	Lower postpartum	Lower postpartum	Numerically fewer (not statistically significant) during first 1/52 in BF.
Davies et al 1989 (168)	N=24 16 BF, 8 AF	1 and 6	BF < AF (assessed by TDD)	Lower postpartum (27%)	↔	Not assessed formally but 10 BF and 1 AF reported increased hypoglycaemia events
Whichelow et al 1983 (167)	N=48 27 BF, 19 AF	12	↔	Lower postpartum	Lower postpartum	N/A

N/A: not assessed: ↔ no significant difference, T1D: type 1 diabetes, controls: non-diabetic women, BF: breastfeeding, AF: artificial feeding, TBR: time below range (<3.9mmol/) as per CGM, TDD: Total daily dose

Glucose monitoring and identification of hypoglycaemia were measured in different ways. Saez-de-Illbarra et al and Riviello et al used capillary blood glucose monitoring, whilst Stage et al identified clinical hypoglycaemia events as self-reported by women (169–171). However as demonstrated by Inkster et al, hypoglycaemia is not always identified by intermittent capillary blood glucose monitoring and during a period where whilst getting used to life with a newborn, additional safety-netting would be useful to prevent potentially harmful maternal hypoglycaemia (172). Interestingly, three recent studies used CGM and reported no difference in hypoglycaemia including overnight between breastfeeding and non-breastfeeding mothers (174,175,177).

4.3.2 Breastfeeding rates in the diabetes population and influencing factors

Breastfeeding rates in the pregestational diabetes population varies from country to country Studies from Denmark and Australia found similar rates of breastfeeding in the type 1 diabetes population compared to that of the general maternity population, whereas studies from Germany and Canada and found lower rates and shorter duration of breastfeeding in mothers with diabetes (170,178–181). The Infant Feeding Survey (IFS), set up in 1975, had been carried out every five years, in the UK. It sought to "provide estimates on the incidence, prevalence, and duration of breastfeeding and other feeding practices adopted by mothers in the first eight to ten months after their baby was born".

The most recent Infant Feeding Survey was conducted in 2010, taking a representative sample of women who registered births during August and September 2010. For this survey, data was collected at three time points: when the babies were four to ten weeks old; when they were four to six months old and when they were eight to ten months old. After the 2010 survey, the Infant Feeding Survey was discontinued. The Infant Feeding Survey (2010) retrieved completed questionnaires at all three time points from 10,768 mothers. The definition of breastfeeding used for reporting was "percentage of all babies who are being breastfed, including being given expressed breastmilk, … even if they are also receiving infant formula, solid food or other liquids". In 2010, the prevalence of breastfeeding across the UK was 55% at six weeks and 34% at six months (182).

Most recent data has been collated for England by the UK Official for Health Improvement and Disparities to produce "annual datasets on the number and proportion of infants who

have been fully, partially or not at all breastfed at 6 to 8 weeks after birth". The most recent dataset: "Breastfeeding at 6 to 8 weeks after birth: annual data April 2022 to March 2023" reported 49.2% of infants were totally or partially breastfed at 6 to 8 weeks postpartum (183).

Several sociodemographic factors influence women's choice of infant feeding method, including maternal age, parity, BMI, socio-economic background and level of educational attainment in addition to pregnancy factors such as gestational age at birth, mode of delivery and admission of the baby to the neonatal intensive care unit (180,184–187). A woman's prior experience of breastfeeding and intention to breastfeed whilst pregnant are also predictors of whether she will attempt and continue breastfeeding (188–190). Women with lower levels of educational attainment, who are younger than 25 years or older than 35 years of age are less likely to express a preference for breastfeeding whilst pregnant (180). Sparud-Lundin et al performed a multivariable analysis suggesting that type 1 diabetes was not an independent factor for breastfeeding. Instead, higher educational level, gestation at delivery (>37 weeks' gestation) and feeding status at discharge and early breastfeeding were predictive of continued breastfeeding at two and six months postpartum (185).

Women with diabetes often experience obstetric and neonatal complications that are associated with a lower chance of initiating and continuing breastfeeding: delivery at an earlier gestation and by caesarean section and the admission of baby to the NICU (neonatal intensive care unit). However, there is also evidence that additional support during pregnancy for example antenatal classes, infant feeding classes and ongoing postnatal support are associated with initiation and ongoing breastfeeding (181,191). In addition, tailored support including exploration of previous breastfeeding experiences, identification of potential contributing factors that may have led to previous unsuccessful breastfeeding attempts and discussion of specific practices such as having easily accessible snacks and hypoglycaemia treatments and identifying someone they can call for support may help women with diabetes to initiate or re-attempt breastfeeding in subsequent pregnancies (181,189,192).

4.3.3 The lived experience of women with type 1 diabetes during the postpartum period

As mothers with diabetes adjust to life with a newborn baby, the additional challenges of managing their diabetes with frequent adjustment of insulin doses and close monitoring of

glucose levels increases mental burden and can negatively impact their transition to motherhood (153). There have been multiple studies describing women's experiences in the weeks to months after giving birth. Women describe the challenges they face managing their glucose levels on the background of weeks to months of changing maternal hormones; the effect of breastfeeding; fear of hypoglycaemia and sudden change and unpredictability daily routine including physical exhaustion and interrupted sleep (31,193). Given the potential risks to themselves and, as a consequence, their baby, women described feeling isolated, exposed and vulnerable especially in the immediate postnatal period once discharged from hospital (193,194).

"Mother 1: I was mostly scared of dropping her on the floor. It was when I was lying down, which is why I didn't see the connection at first.... I'm sort of tired. I had her on my outer side near the edge of the couch but somehow I've always managed to keep a hold of her. And she had fallen asleep because she was full and happy. And then her kicking me and crying woke me up. That didn't feel safe at all." (193)

This split in attention between diabetes self-management and constant care of their newborn is also described as leading to resentment and frustration with having the condition (31).

"It's so tough, because I have all the symptoms that come with low blood glucose—I'm trembling and weak and a little dizzy, and at the same time taking care of the needs of a small child. Then it's also emotionally hard. I get angry because I feel that it's so hard to have diabetes and at the same time ... I have never been so angry at the fact that I have diabetes as since he came into my life. Because it doesn't fit (laughs). It is disturbing. It disturbs my focus on him. I have to prioritize between two things which I cannot prioritize between." (31)

In addition, the conflicting balance between caring for diabetes and their baby; feeling of isolation and vulnerability; and overall heavy mental burden can lead to psychosocial issues. Studies report worsened depressive symptoms in women with type 1 diabetes after delivery compared to during the third trimester and higher levels of worry over the first six months' postpartum compared to mothers without diabetes (135,190).

"I have always had a really positive outlook on life but, since having my daughter, I seem to be worrying about my health all of the time. But the whole thing could be psychological

because I am worrying so much. I am just scared of the future, I'm scared of being sick and in pain and of dying early. There is nothing happening health wise that I am worried about right now though, I am just worrying about things that 'might' happen later on"(194)

"I don't know what is going on. I feel very depressed, crying a lot. I just feel I have no-one to talk to or understand. My husband is there but I feel he can't really understand what it's like to know that this isn't going away ever" (194)

When unable to balance the two, women described deprioritising their diabetes self-management in order to better meet their baby's needs and / or experience a loss of motivation to continue managing their diabetes (193,194).

"Sometimes I really don't care if I take the insulin, then I realise if I don't get my [blood] sugar under control I will not be around for my boys (they are 17 months and 3 years old)" (194)

This challenging period of transition was also accompanied with a gap in care and loss of professional support for sometimes as long as six months as women were transferred from specialist diabetes antenatal services to general adult diabetes services and the frequency of follow up reduces from every two to four weeks to once or twice a year (31,152,193). Linden et al described a lower sense of coherence: "a person's view of life and capacity to respond to stressful situations", when they felt there was a difference in a woman's need for professional medical support and the amount they were able to access and receive (195).

Once I was postnatal they [the health professionals] all ditched me. When the baby is born it is all over [referring to services and health professionals]. I was left behind after giving birth. You can feel helpless with a new baby. I have no family around me and my husband is working all day. It is very hard and no health professional seems to care (152)

When they did access medical support during the postpartum period, women described the importance of accurate and compassionate specialist advice in relation to their diabetes during the postpartum period. They described a loss of faith and distrust when their changing needs and priorities were not acknowledged (193). Conversely, women also described feeling proud and happy during motherhood when they did fell well supported (by both

healthcare professionals, friends and family) and were able to maintain a strong drive to succeed and establish breastfeeding (190,194).

4.3.4 Hybrid closed-loop systems in the postpartum period

Type 1 diabetes management has been revolutionised by the development of hybrid closed-loop systems. Their use has become more widespread as studies report effectiveness both for helping users meet glycaemic targets and for reducing the mental burden of diabetes self-management across adult, paediatric and pregnancy populations (79,80,139,143). In December 2023, the UK National Institute for Health and Care Excellence (NICE) updated its guidance for diabetes technology use. Following the AiDAPT study (Automated insulin Delivery Amongst Pregnant women with Type 1 diabetes, ISRCTN56898625), the NICE Technology Appraisal [TA943] now recommends offering hybrid closed-loop therapy use before and during pregnancy (196).

By contrast, despite its unique challenges, current guidelines do not specifically address the postnatal period with respect to diabetes management or technology use. There have been four small studies and five case series that have examined postpartum use of commercially available hybrid closed-loop systems (86–88,97,100,101,177,197,198). However, the evidence base is too limited in scope and size inform and direct current diabetes guidance regarding the use of diabetes technologies and hybrid closed-loop therapy use during the postpartum period. As more women use hybrid closed-loop before and during type 1 diabetes pregnancy, this omission and gap in postpartum diabetes management requires urgent attention, so that women are empowered to choose evidence-based therapy during this challenging period.

Out of the four studies (Table 4.2), the two UK Closed-Loop in Pregnancy (CLIP-03, CLIP-04) studies examined previous prototype versions of the CamAPS FX system whilst the American Pregnancy Intervention with a Closed-Loop System (PICLS) study and Canadian Closed-Loop Insulin in Mothers with Type 1 Diabetes and Baby feeding practices (CLIMB) study examined the Medtronic MiniMed 670G and 770G hybrid closed-loop systems (86–88,197,198). In the two UK studies and the American study, hybrid closed-loop use was started during pregnancy and continued postnatally. In the Canadian study, hybrid closed-loop therapy was started de-novo one week after birth.

The UK CLIP studies reported safe inpatient use of previous prototype versions of the CamAPS FX system in 27 participants throughout labour, birth and the initial 48-hours postpartum (88). CLIP-04 also examined glycaemic outcomes in 12 participants who opted to continue CamAPS FX use for a further six weeks after giving birth and described target glycaemic attainment (77% time in target range, 3.9-10.0mmol/L) with low rates of maternal hypoglycaemia (2.4%) (87).

Table 4.2 Studies evaluating hybrid-closed loop use during the postnatal period

Study*	**Number of participants and HCL system**	**Duration of follow up postpartum**	**Timing of HCL initiation**
Stewart et al 2018 (Secondary analyses from CLIP-03 and CLIP-04) (88)	N = 27 HCL (Prototype CamAPS FX)	48 hours	Continuation from pregnancy
Stewart et al 2018 (CLIP-04) (87)	N = 12 HCL (Prototype CamAPS FX)	6 weeks	Continuation from pregnancy
Donovan et al 2023 (CLIMB RCT) (197)	N = 9 HCL (Medtronic Minimed 670G and 770G) N = 9 open-loop insulin pump therapy with predictive low glucose suspend function (all 18 for continuation phase)	Randomised phase weeks 1-12 then further 12 week continuation	Week one postpartum
Polsky et al 2024 (PICLS RCT) (198)	N = 11 HCL (Medtronic Minimed 670G) N = 12 open-loop insulin pump therapy	4-6 weeks	Continuation from pregnancy

***** CLIP = Closed-Loop in Pregnancy studies, CLIMB = Closed-Loop Insulin in Mothers with Type 1 Diabetes and Baby feeding practices study, PICLS = Pregnancy Intervention with a Closed-Loop System study, RCT = randomised controlled trial, HCL = hybrid closed-loop therapy

The Canadian CLIMB study of 18 participants and American PICLS study of 23 participants reported similar glycaemic outcomes: CLIMB time in range 79% vs 78% (hybrid closed-loop vs. open-loop insulin pump therapy) and PICLS time in range 75% vs 77% respectively, associated with the use of the Medtronic MiniMed 670G and 770G hybrid closed-loop

systems (197,198). Interestingly, CLIMB participants randomised to the open-loop insulin pump therapy (control) arm, were permitted to continuing using the predictive low suspend glucose feature of the pump whereas PICLS control arm participants were instructed not to use this function. The CLIMB and PICLS studies also reported low rates of maternal hypoglycaemia: 2% vs 6% and 5% vs 9% respectively (hybrid closed-loop vs. open-loop insulin pump therapy). Whilst reassuring from a safety perspective, these feasibility studies do not demonstrate definitive proof of efficacy. They also included participants with near optimal glycaemia which limits their generalisability, in real-world settings.

There have been two studies that have explored women's experiences of using hybrid closed-loop in postnatal period (101,199). The first was a case series of four women who were "early adopters" of Tandem Control-IQ hybrid-closed loop system use during pregnancy up to six weeks postpartum (101). In interviews during the first six weeks postpartum, they described less disruption in sleep from their diabetes as they were reassured that the system would manage their glucose levels for them without the need to wake to check or correct as they would have done on their previous insulin therapies (open-loop insulin pump therapy or multiple daily injections). This reassurance also meant that they were able to spend more time with their newborn. They also described challenges related to general pump use such as infusion set failures and the tube of the cannula getting caught or pulled by their baby especially during breastfeeding.

A further study involved semi-structured interviews of 16 participants using the Medtronic Minimed 670G and 770G systems from the Canadian CLIMB study and some of their partners at 12 and 24 weeks after delivery (199). Quintanilha et al reported that whilst helpful to prevent low glucose levels, the women were often frustrated with what they perceived to be a lack of aggressiveness of the hybrid closed-loop algorithm when managing the higher glucose levels. Some participants reported using "phantom" or "fake carbs" to manipulate the system into administering more insulin in order to bring down their glucose levels more quickly and to a level acceptable to them. A further frustration that postpartum mothers experienced was that there did not seem to be much distinction between different alerts from the system: whether it be to calibrate the sensor or system; an empty reservoir or suspended delivery "you seem to only get one alarm for that". Most women also noted that their baby and their needs were the priority and instead of the method of insulin delivery impacting their choice or form of infant feeding.

"Oh, like I didn't pre bolus because I didn't have enough time to but now's an opportunity to eat so I'm just going to eat. So, it's kind of like I'm working around her schedule" (199)

In summary, maternal glycaemia in the postnatal period is complicated by many contributing factors. With the glycaemic benefits associated with use of hybrid closed-loop therapy in other populations and during pregnancy, we hypothesised that these benefits may also be conferred to mothers during the postpartum period after having a baby. This study examines the continued use of the CamAPS FX hybrid closed-loop system from pregnancy and its effects on maternal glycaemia from day one following delivery throughout the first six months postpartum and whether there were any changes in treatment effect during the earlier (0 to <3 months) or later (3 to 6 months) postpartum period. It also seeks to capture the diabetes and treatment-related lived experience of women over this time.

4.4 Methods

4.4.1 Study design

This study was performed as an extension to AiDAPT (Automated insulin Delivery Amongst Pregnant women with Type 1 diabetes, ISRCTN56898625), a multicentre, parallel group, randomised controlled trial, recruiting pregnant women with T1D across nine NHS sites across the UK. During AiDAPT, participants were randomly assigned during pregnancy to receive the intervention: hybrid closed-loop therapy (CamAPS FX system) or to standard care: continuation of their standard insulin therapy (multiple daily injections or insulin pump) together with CGM. The AiDAPT study protocol is included in the Appendix of this thesis and primary biomedical and psychosocial results previously presented in Chapter 2. Both have previously been published and are briefly summarised below (83,139).

In the initial AiDAPT study design, women were provided with a further three to four sensors after delivery to allow for a six to eight weeks of postpartum CGM to facilitate safe transition back to usual NHS clinical care. However, in December 2020, approximately halfway through recruitment, the NICE Diabetes in Pregnancy guidelines were updated to recommend 12 months of real-time CGM use for all pregnant women with type 1 diabetes (34,200). This was accompanied by national ring-fenced pregnancy funding to accelerate nationwide implementation during 2021 (201). This meant that pregnant women with type 1 diabetes

who did not participate in the AiDAPT study were allocated up to six months of NHS-funded postnatal CGM (based on women starting CGM at 10-12 weeks' gestation and delivering around 36-38 weeks' gestation). This raised an ethical dilemma where AiDAPT trial participants were potentially disadvantaged as at that point they could only access six to eight weeks of postnatal CGM use.

Additional changes in maternity and diabetes service provision during and after the COVID-19 pandemic included increased clinical pressures among trial staff and restricted face-to-face appointments. As a result, Research Ethics Committee approval was sought to extend the use of CGM with or without hybrid closed-loop therapy for eligible trial participants for six months postpartum. This was approved (AiDAPT protocol version 5.0, included in the Appendix of this thesis) to comply with national CGM recommendations and ensure safe postnatal transition for the remaining AiDAPT participants. Registration of the postpartum extension study was included in the AiDAPT trial registration (ISRCTN56898625) and the protocol was previously described in the published study protocol paper (83).

4.4.2 Trial participants

Pregnant women aged 18 to 45 years of age, with at least a one year duration of type 1 diabetes and a HbA1c of 48 to ≤86 mmol/mol were recruited to AiDAPT prior to 14 weeks' gestation. Those recruited after implementation of the postpartum protocol amendment (AiDAPT protocol version 5.0, 12th November 2021) or those still pregnant or within six months of delivery at the time of amendment implementation were eligible for inclusion in postpartum follow up extension study.

4.4.3 Randomisation and Masking

Participants continued their assigned treatments following randomisation in early pregnancy (median ~11 weeks' gestation). They were randomised on a 1:1 basis with stratification by clinical site using a computer-generated randomisation system with randomly permuted blocks sizes of 2 and 4. Once a participant was randomised, both the investigator and participant were aware of the treatment assignment. Investigators were masked to the results until the study was completed. The primary outcome was based on the downloaded CGM data. Statisticians at the coordinating centre (Jaeb Center for Health Research) who had

access to the CGM data and analysed glycaemic outcomes were not masked to the study treatment allocation.

4.4.4 Trial procedures

Eligible participants at the time of implementation of the postpartum protocol amendment (those still pregnant or within 6 months of delivery and for whom CGM data were available) were approached to re-consent for the postpartum extension. Those recruited after implementation of the postpartum amendment were consented at the same time as recruitment to the AiDAPT trial. Following delivery of their babies, participants in both groups received usual NHS clinical care.

4.4.5 Treatments

Hybrid closed-loop group

The hybrid closed-loop system used was as per the AIDAPT trial i.e. the CamAPS FX application (version 0.3.71, CamDiab, Cambridge, UK), hosted on an android smartphone (Samsung Galaxy S8-S12, Samsung, Suwon-si, South Korea). A Dana Diabecare RS insulin pump (Sooil, Seoul, South Korea) and Dexcom G6 CGM (Dexcom, San Diego, USA) communicated by Bluetooth with the algorithm for insulin administration and glucose monitoring respectively. Postnatal plans with starting guidance for pump and hybrid closed-loop system settings were agreed between the woman and diabetes antenatal teams and documented prior to delivery, around 36 weeks' gestation. Women were advised to switch to recommended starting postpartum settings immediately before caesarean section or as soon as the placenta delivered.

Recommended initial postpartum settings included a personal glucose target of 6.0mmol/L and insulin to carbohydrate ratios of between 1:12g and 1:15g depending on infant feeding intention. Following delivery, whilst still in hospital, participants titrated their own personal glucose targets, insulin-to-carbohydrate ratios and pre-meal insulin doses aiming for International Consensus on Time in Range CGM targets (70% time between 3.9 - 10.0mmol/L and <5% time below 3.9mmol/L). Women were also encouraged to use the "Boost" and/or "Ease off" features for at least 2-4 hours at a time if they felt that other setting changes were not fast enough to counter higher or lower glucose levels. They were encouraged to continue self-titrating their settings as needed when discharged from hospital

with contact details for their usual NHS diabetes clinical support (adult diabetes services including diabetes specialist nurses and midwives), given the variable nature of insulin dosing and requirements between individuals and from day-to-day (202).

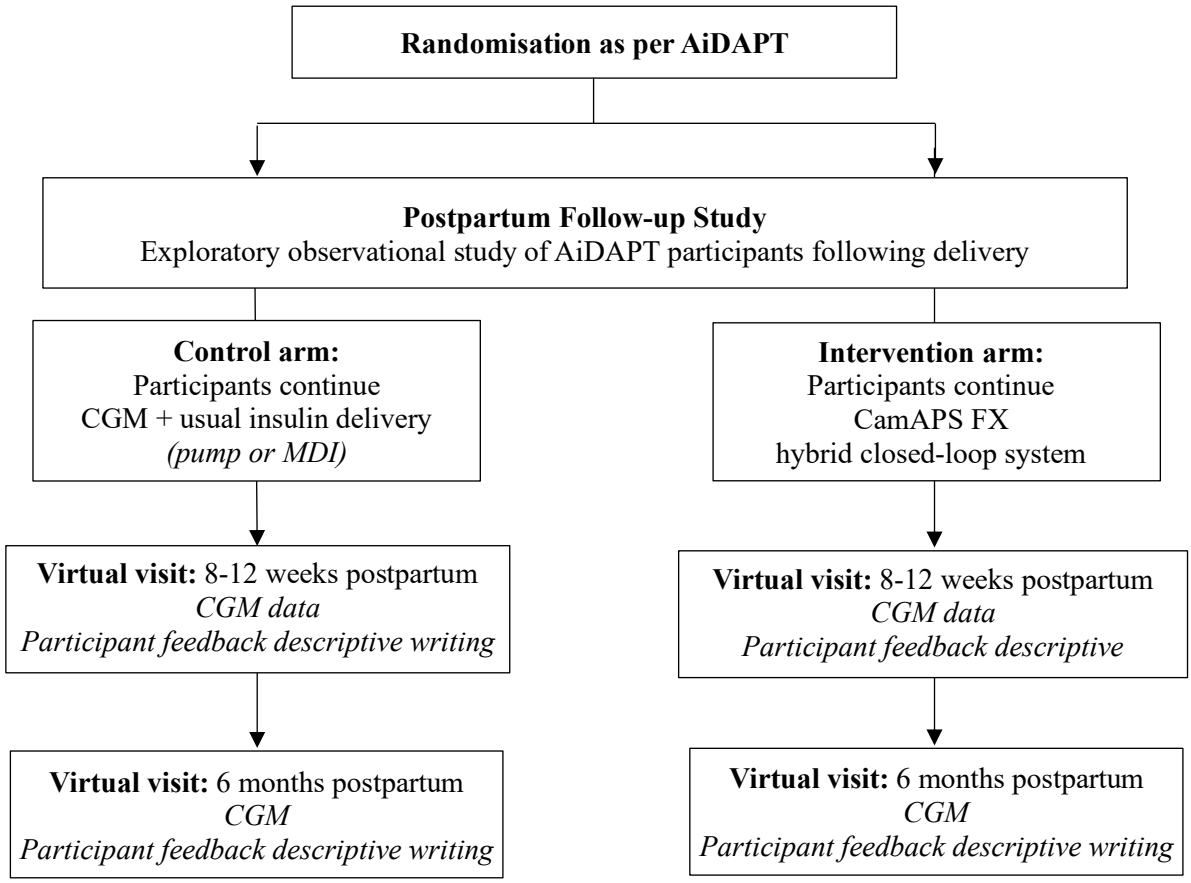
Standard Care Group

Participants assigned to the standard care group continued their usual insulin therapy, multiple daily injections or insulin pump therapy, with clinical support from their local teams. During the postpartum period, insulin doses (both pre-meal insulin boluses and basal insulin doses) were titrated to achieve International Consensus on Time in Range CGM targets (70% time between 3.9 - 10.0mmol/L).

4.4.6 Postpartum visits

Participants were followed up by telephone at 8-12 and 24 weeks after delivery, at which CGM data, insulin delivery method and doses, safety outcomes and infant feeding status were reviewed (Figure 4.1). Participants received review of their diabetes management with adjustments to insulin dosing and advice if required. At each visit, participants were also sent open ended questions to provide self-reported free text feedback on their diabetes and treatment-related lived experiences.

Figure 4.1 Flow of participants through the postpartum study



4.4.7 Outcomes

Primary outcome was the between-group difference in percentage of time with CGM glucose levels in the postpartum (non-pregnancy) target glucose range; 3.9-10.0mmol/L. The six-month postpartum extension was split into two periods: from the day of delivery to three months and from three months to six months post-delivery. In each three-month period, CGM outcomes were calculated overall and by time of day (day: 7am-11pm, night: 11pm-7am). Pre-specified secondary outcomes were percentage of time spent hyperglycaemic (>10.0mmol/L) and hypoglycaemic (<3.9mol/L) and other sensor glucose metrics (mean CGM glucose and glucose variability metrics). Safety outcomes were severe hypoglycaemia, diabetic ketoacidosis and device-related adverse events (or adverse device events). Adverse device events are defined as adverse events related to the use of an investigational medical device including user error. In this study, relation to the investigational medical device was further characterised to the corresponding contributing components i.e. the CGM sensor or connectivity, insulin pump connectivity or pump cannula set failures or the hybrid-closed loop algorithm itself.

4.4.8 Statistical Analyses

A minimum of 300 hours of CGM data in each 3-month period were required to calculate overall CGM outcomes, and a minimum of 200 and 100 hours of CGM data were required to calculate daytime and overnight CGM outcomes, respectively.

A repeated measures linear regression model was fit for the 3-month period outcomes, with CGM outcome as the dependent variable adjusting for pre-pregnancy insulin delivery method (insulin pump or multiple daily injections), CGM metrics during the baseline pre-randomisation run-in period (approximately 10-11 weeks' gestation), and clinical site as a random effect. A point estimate and 95% confidence interval were calculated for the adjusted treatment difference based on the linear regression model. A two-sided p-value was calculated for the treatment effect based on the linear regression model, and a 5% level was used to declare statistical significance. Residual values were examined for an approximate normal distribution. If values were highly skewed, the model used a t distribution with 10 degrees of freedom for the errors. The same model was repeated with an interaction between postpartum period (0 to <3 months, and 3 to 6 months) and treatment group to examine if the treatment effect changed depending on postpartum period.

There was no imputation for missing data. The false discovery rate was controlled using the adaptive Benjamini-Hochberg procedure for multiple comparisons. Analyses were performed with the use of SAS, version 9.4.

4.4.9 Qualitative Methods

To assess diabetes and treatment-related lived experience as described through self-reported free text feedback, women were sent the following questions to answer.

At the 8-12 week postpartum virtual follow up visit:
"Thinking about your use of the CGM or closed-loop artificial pancreas, please could you tell us what impact you think it had on the following areas:

- Your feelings about your blood glucose levels, if you used the CGM or closed-loop system, in the six weeks after giving birth
- Thoughts around safety for your health and the health of your baby if you used the CGM or closed-loop, in the six weeks after giving birth"

At the 24 week (6 month) postpartum virtual follow up visit:
"Thinking about your use of the CGM or closed-loop artificial pancreas, please could you tell us what impact you think it had on the following areas:

- Your feelings about your blood glucose levels, if you used the CGM or closed-loop system, in the six months after giving birth
- Thoughts around safety for your health and the health of your baby if you used the CGM or closed-loop, in the six months after giving birth"

Data analysis

Data analysis sought to identify descriptive and analytical themes with relevance to clinical practice. The written responses from control and intervention participants were separated and then read through and cross-compared to identify common themes. Coding was used to capture data relevant to each of these themes and subsequent coded reports were used to identify quotes. Qualitative software (Qualcoder version 3.5) was used to facilitate data coding and retrieval for the qualitative analysis of the lived experience data.

4.5 Results

Participants

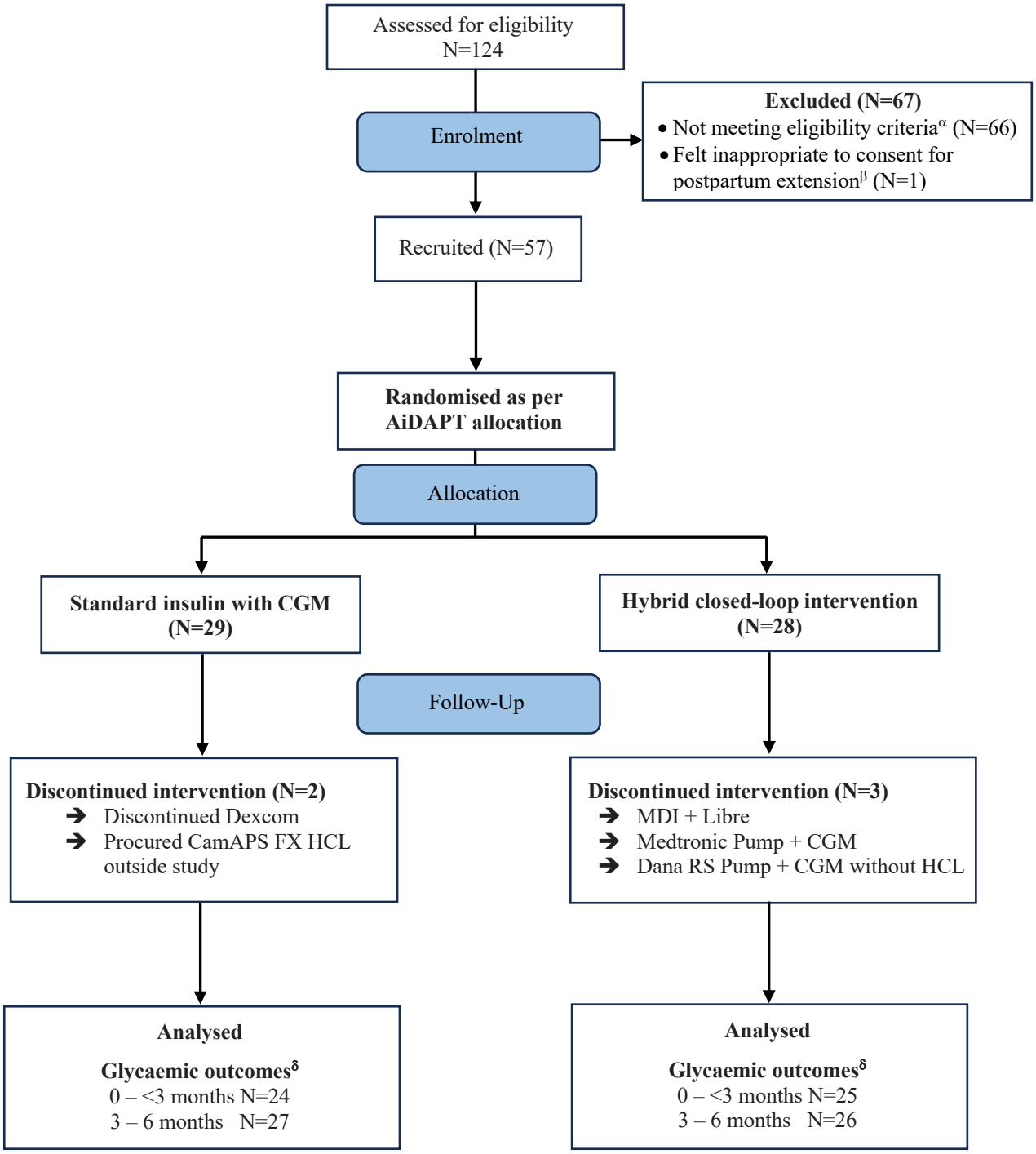
Out of the entire 124 AiDAPT trial participants, 66 were not eligible for inclusion in the postpartum extension study. 60 participants (91%) were ineligible because they were already over 6 months postpartum when ethical and regulatory approvals were implemented at trial sites. A further six participants (9%) were ineligible because they had already discontinued either hybrid closed-loop or control interventions (standard insulin therapy with CGM) despite being within 6 months postpartum. One control arm participant had a neonatal death and it was deemed inappropriate by trial team and site investigators to approach and re-consent her for the postpartum study (Figure 4.2).

57 participants consented to continue their randomised allocation (standard care, comprising of CGM with multiple daily injections or insulin pump therapy vs hybrid closed-loop therapy) into the postpartum extension study. Postnatal participants were recruited from nine NHS clinical sites, spanning England, Scotland and Northern Ireland. At booking, participants had a mean (± SD) age of 31 ± 4years, 50 (88%) or participants were White, and had an early pregnancy baseline HbA1c of 59.4 ± 10.5mmol/mol (Table 4.3). Participants in

both groups spent approximately 70% time in range (3.9 - 10.0mmol/mol) at baseline during early pregnancy before randomisation (Table 4.5). Participant baseline characteristics for those who consented to continue in the postpartum extension were compared to those who were ineligible or not included and were found to be similar (Table 4.4).

In the standard care group, there were more participants for whom this was their first pregnancy, started pregnancy with a lower maternal BMI, gained more weight during pregnancy and were more likely to deliver by primary caesarean section (Table 4.3). During pregnancy, from 16 weeks' gestation until delivery, AiDAPT participants in the hybrid closed-loop group spent more time in the pregnancy-specific target range of 3.5-7.8mmol/L compared to those in the standard care group: 68% compared to 56% (139). This was similar in those who went on to participate in the postpartum extension: 67% (hybrid closed-loop) vs 58% (standard care) (Table 4.3).

Figure 4.2 Consort diagram



α Reasons for not meeting trial eligibility criteria (N=66) were:
- Participants more than 6 months postpartum (N=60)
- Completed the study and returned to NHS care prior to extension being implemented and so these participants were no longer using hybrid closed-loop (CamAPS FX) or continuous glucose monitoring (Dexcom G6). (N=6)

β This participant had a neonatal death and it was felt by both trial team and local site investigators inappropriate to approach to continue into postnatal extension.

δ In the hybrid closed-loop group, three participants had missing data in the 0-<3 months period and two had missing data in the 3-6 months period as assessed by continuous glucose monitoring. In the standard care group, five participants had missing data in the 0-<3 months period and two had missing data in the 3-6 months period as assessed by continuous glucose monitoring (CGM).

Table 4.3 Participant baseline characteristics

	Hybrid closed-loop (N = 28)	**Standard care (N = 29)**	**Overall (N = 57)**
Age (years) mean ± SD	32 ± 4	30 ± 4	31 ± 4
Race / Ethnicity[α]			
White	25 (89%)	25 (86%)	50 (88%)
Black	1 (4%)	2 (7%)	3 (5%)
Asian	1 (4%)	1 (3%)	2 (4%)
Other / More than one race	1 (4%)	1 (3%)	2 (4%)
Booking BMI (kg/m^2)[β] mean ± SD	28.6 ± 4.5	25.8 ± 3.9	27.2 ± 4.4
Education			
Secondary education	3 (11%)	5 (17%)	8 (14%)
Further education	8 (29%)	9 (31%)	17 (30%)
University undergraduate degree or equivalent	14 (50%)	11 (38%)	25 (44%)
University postgraduate degree or equivalent	3 (11%)	4 (14%)	7 (12%)
Previous pregnancies >24 weeks' gestation			
0	7 (25%)	16 (55%)	23 (40%)
1	13 (46%)	11 (38%)	24 (42%)
2	6 (21%)	1 (3%)	7 (12%)
≥3	2 (7%)	1 (3%)	3 (5%)
Diabetes duration (years) mean ± SD	17 ± 8	16 ± 7	16 ± 7
HbA1c during early pregnancy mean ± SD			
mmol/mol	59.5 ± 11.6	59.3 ± 9.5	59.4 ± 10.5
Diabetes complications	15 (54%)	17 (59%)	32 (56%)
Early pregnancy insulin modality			
Pump	15 (54%)	11 (38%)	26 (46%)
Multiple dose injections	12 (43%)	17 (59%)	29 (51%)
Automated insulin delivery[ϕ]	1 (4%)	1 (3%)	2 (4%)
Adverse events pre-pregnancy, previous 12 months No. of participants (quartiles)			
Pre-pregnancy DKA	0 (0%)	3 (10%)	3 (5%)
Previous severe hypoglycaemia[δ]	1 (4%)	2 (7%)	3 (5%)
%Time in range 3.5 – 7.8mmol/L during pregnancy[λ] mean ± SD	67% ± 8%	58% ± 11%	62% ± 11%
Median % time CGM use[λ] (quartiles)	96% (82%, 98%)	97% (94%, 98%)	97% (91%, 98%)
Adverse events during pregnancy[λ] (No. of events)			
Severe hypoglycaemia during pregnancy	5	1	6
DKA during pregnancy	1	1	2
Maternal gestational weight gain (kg) mean ± SD	11.5 ± 6.1	15.3 ± 6.0	13.4 ± 6.3
Gestation at delivery mean ± SD	36.6 ± 1.7	37.0 ± 1.1	36.8 ± 1.4

Mode of delivery			
Operative Vaginal	2 (7%)	2 (7%)	4 (7%)
Primary caesarean	8 (29%)	18 (62%)	26 (46%)
Repeat caesarean	14 (50%)	7 (24%)	21 (37%)
Vaginal	4 (14%)	2 (7%)	6 (11%)

Number (%) unless otherwise stated.

α Race / ethnicity was reported by the participant.

β Maternal BMI calculated with maternal weight at first medical appointment in pregnancy (booking appointment)

ϕ Participants using alternative hybrid closed-loop systems were eligible.

δ Hypoglycaemia was considered severe if the event required third-party assistance.

λ 16 weeks' until delivery

Table 4.4 Characteristics of included and ineligible postpartum study participants

	Postpartum Participants		Ineligible Participants[α]	
	Hybrid closed-loop (N = 28)	**Standard care (N = 29)**	**Hybrid closed-loop (N = 33)**	**Standard care (N = 34)**
Age (years) mean ± SD	32 ± 4	30 ± 4	32 ± 6	30 ± 6
Race / Ethnicity[β]				
White	25 (89%)	25 (86%)	33 (100%)	32 (94%)
Black	1 (4%)	2 (7%)	0 (0%)	1 (3%)
Asian	1 (4%)	1 (3%)	0 (0%)	1 (3%)
Other/More than one race	1 (4%)	1 (3%)	0 (0%)	0 (0%)
Booking BMI (kg/m^2)[ϕ] mean ± SD	28.6 ± 4.5	25.8 ± 3.9	27.3 ± 6.8	27.9 ± 5.3
Education				
Secondary education	3 (11%)	5 (17%)	4 (12%)	5 (15%)
Further education	8 (29%)	9 (31%)	10 (30%)	11 (32%)
University undergraduate degree or equivalent	14 (50%)	11 (38%)	11 (33%)	13 (38%)
University postgraduate degree or equivalent	3 (11%)	4 (14%)	8 (24%)	5 (15%)
Previous pregnancies >24 weeks' gestation				
0	7 (25%)	16 (55%)	14 (42%)	22 (65%)
1	13 (46%)	11 (38%)	10 (30%)	10 (29%)
2	6 (21%)	1 (3%)	8 (24%)	2 (6%)
≥3	2 (7%)	1 (3%)	3 (5%)	0 (0%)
Diabetes duration (years) mean ± SD	17 ± 8	16 ± 7	19 ± 8	16 ± 8
HbA1c during early pregnancy mean ± SD (mmol/mol)	59.5 ± 11.6	59.3 ± 9.5	59.1 ± 12.7	65.8 ± 16.1
Diabetes complications	15 (54%)	17 (59%)	20 (61%)	18 (53%)
Early pregnancy insulin modality				
Pump	15 (54%)	11 (38%)	17 (52%)	14 (41%)
Multiple dose injections	12 (43%)	17 (59%)	15 (45%)	20 (59%)
Automated insulin delivery[δ]	1 (4%)	1 (3%)	1 (3%)	0
Adverse events pre-pregnancy, previous 12 months				
Pre-pregnancy DKA	0 (0%)	3 (10%)	1 (3%)	7 (21%)
Previous severe hypoglycaemia[λ]	1 (4%)	2 (7%)	3 (9%)	3 (9%)
%Time in range 3.5-7.8mmol/L during pregnancy[π] mean ± SD	67% ± 8%	58% ± 11%	69% ± 12%	54% ± 14%
Median % Time CGM use during pregnancy[π] (quartiles)	96% (82%, 98%)	97% (94%, 98%)	97% (96%, 98%)	95% (90%, 98%)
Maternal gestational weight gain (kg) mean ± SD	11.5 ± 6.1	15.3 ± 6.0	10.7 ± 6.2	12.4 ± 6.0
Gestation at delivery mean ± SD	36.6 ± 1.7	37.0 ± 1.1	36.4 ± 1.7	37.2 ± 1.3

Mode of delivery				
Pregnancy loss	0 (0%)	0 (0%)	2 (6%)	3 (9%)
Operative Vaginal	2 (7%)	2 (7%)	1 (3%)	3 (9%)
Primary caesarean	8 (29%)	18 (62%)	16 (48%)	16 (47%)
Repeat caesarean	14 (50%)	7 (24%)	11 (33%)	4 (12%)
Vaginal	4 (14%)	2 (7%)	3 (9%)	8 (24%)

Number (%) unless otherwise stated.

α Reasons for not meeting trial eligibility criteria were:

- Participants more than 6 months postpartum (N=60)
- Completed the study and returned to NHS care prior to extension being implemented and so these participants were no longer using hybrid closed-loop (CamAPS FX) or continuous glucose monitoring (Dexcom G6). (N=6)

This also includes a participant who had a neonatal death and it was felt by both trial team and local site investigators inappropriate to approach to continue into postnatal extension.

β Race / ethnicity was reported by the participant.

ϕ Maternal BMI calculated with maternal weight at first medical appointment in pregnancy (booking appointment)

δ Participants using alternative hybrid closed-loop systems were eligible.

λ Hypoglycaemia was considered severe if the event required third-party assistance.

π 16 weeks' until delivery

Five participants in the postpartum extension did not adhere to their assigned treatment (Figure 4.2). Three intervention group participants discontinued CamAPS FX hybrid closed-loop use: one stopped using the Dana RS study pump and recommenced her previous Medtronic pump; one experienced increased personal and social difficulties affecting her ability to continue hybrid closed-loop use; and one reverted back to multiple daily injections around three months postpartum after experiencing multiple Dana RS pump infusion set failures. From the standard care group, one participant discontinued Dexcom CGM after delivery and another accessed and self-funded hybrid closed-loop therapy (CamAPS FX) which she started during early pregnancy (post-randomisation) and continued throughout the six month postpartum study.

All available periods with CGM data were included in the models. One participant was missing baseline CGM data. In the hybrid closed-loop group, two participants were missing data in the 0-<3 months period and three were missing data in the 3-6 months period as assessed by CGM. In the standard care group, two participants were missing data in the 0-<3 months period and five were missing data in the 3-6 months period as assessed by CGM (Figure 4.2).

Glycaemic outcomes

Hybrid closed-loop users maintained mean percentage time in range (3.9-10.0mmol/L) from 73 ± 14% in early pregnancy (baseline run-in prior to randomisation) to 72 ± 12% throughout the six-month postpartum period (Table 4.5). For standard care participants, percentage time spent in target range decreased from 70 ± 13% in early pregnancy to 54 ± 17% during the six-months postpartum period. The mean adjusted treatment difference between the hybrid closed-loop intervention and standard care control group was 15% (95% CI 7 to 22%). Differences in glycaemia were apparent from the first four weeks postpartum and in each subsequent four-week period following delivery, with consistently higher time in range for the hybrid closed-loop group (Figure 4.3). Post hoc analysis of maternal glycaemia over the first 2 weeks postpartum starting from the day of delivery (requested during peer review) demonstrated the immediate impact of hybrid closed-loop use: time in range 80% (hybrid closed-loop therapy) vs 67% (standard insulin therapy with CGM) (Table 4.6).

Table 4.5 Postnatal maternal glycaemic outcomes by treatment group and 3-month postpartum period

Outcomes	RCT Baseline[α]		Postpartum[β]		Adjusted Treatment Difference[δ] (95% CI)	P-value for Treatment Effect[δ]	P-value for Interaction[δ]
	Hybrid closed-loop	Standard care	Hybrid closed-loop	Standard care			
Hours of CGM Data			3,893 ± 622	3,636 ± 989			
Number of participants[ϕ]							
0-<3 months	N=26	N=27	N=26	N=27			
3-6 months	N=25	N=24	N=25	N=24			
% Time 3.9-10.0mmol/L	73% ± 14%	70% ± 13%	72% ± 12%	54% ± 17%	15% (7%, 22%)	0.0037	0.83
0-<3 months	73% ± 14%	70% ± 13%	75% ± 12%	57% ± 16%	15% (7%, 23%)		
3-6 months	74% ± 13%	72% ± 13%	70% ± 9%	50% ± 19%	16% (7%, 24%)		
% Time 3.9-7.8mmol/L	50% ± 15%	47% ± 12%	51% ± 11%	33% ± 13%	-	-	-
0-<3 months	50% ± 15%	47% ± 12%	54% ± 12%	35% ± 12%	-		
3-6 months	51% ± 15%	48% ± 12%	48% ± 10%	30% ± 15%	-		
Mean glucose (mmol/L)	7.9 ± 1.3	7.9 ± 1.0	8.5 ± 1.5	10.0 ± 2.0	-1.3 (-2.3, -0.3)	0.036	0.78
0-<3 months	7.9 ± 1.3	7.9 ± 1.0	8.2 ± 1.5	9.7 ± 1.9	-1.3 (-2.2, -0.3)		
3-6 months	7.8 ± 1.3	7.8 ± 1.0	8.6 ± 1.0	10.5 ± 2.4	-1.5 (-2.6, -0.3)		
% Time >10.0mmol/L	22% ± 15%	22% ± 12%	26% ± 12%	42% ± 18%	-14% (-23%, -6%)	0.0055	0.78
0-<3 months	22% ± 15%	22% ± 12%	22% ± 13%	39% ± 17%	-15% (-23%, -6%)		
3-6 months	21% ± 15%	21% ± 12%	28% ± 10%	47% ± 21%	-15% (-25%, -6%)		

Median % Time >13.9mmol/L	3% (1%, 9%)	3% (1%, 7%)	7% (3%, 11%)	15% (8%, 30%)	-9% (-16%, -2%)	0.029	0.18
0-<3 months	3% (1%, 9%)	3% (1%, 7%)	4% (2%, 10%)	13% (6%, 22%)	-9% (-16%, -2%)		
3-6 months	2% (1%, 7%)	2% (1%, 6%)	8% (4%, 12%)	19% (9%, 37%)	-12% (-20%, -3%)		
Median % Time <3.9mmol/L	5.0% (3.1%, 6.8%)	4.6% (2.3%, 11.8%)	2.4% (1.5%, 4.0%)	2.6% (1.4%, 5.2%)	-0.7% (-2.0%, 0.5%)	0.49	0.78
0-<3 months	5.0% (3.1%, 6.8%)	4.6% (2.3%, 11.8%)	2.5% (1.4%, 4.3%)	2.2% (1.1%, 6.0%)	-0.8% (-2.2%, 0.6%)		
3-6 months	4.9% (3.1%, 6.8%)	4.0% (2.3%, 12.9%)	2.3% (1.6%, 3.7%)	2.9% (2.0%, 5.0%)	-0.6% (-2.0%, 0.7%)		
Median % Time <3.0mmol/L	1.2% (0.2%, 2.2%)	0.7% (0.3%, 3.1%)	0.4% (0.3%, 0.6%)	0.6% (0.2%, 1.3%)	-0.2% (-0.6%, 0.1%)	0.33	0.78
0-<3 months	1.2% (0.2%, 2.2%)	0.7% (0.3%, 3.1%)	0.4% (0.3%, 0.7%)	0.6% (0.2%, 1.2%)	-0.3% (-0.8%, 0.1%)		
3-6 months	1.0% (0.2%, 2.2%)	0.6% (0.3%, 3.1%)	0.4% (0.2%, 0.7%)	0.5% (0.2%, 1.5%)	-0.2% (-0.6%, 0.1%)		
Glucose CV (%)	36% ± 6%	37% ± 7%	39% ± 4%	40% ± 5%	0% (-2%, 3%)	0.012	0.019
0-<3 months	36% ± 6%	37% ± 7%	37% ± 5%	40% ± 6%	-1% (-4%, 1%)		
3-6 months	35% ± 5%	36% ± 7%	39% ± 4%	39% ± 6%	2% (-1%, 5%)		
Glucose SD (mmol/L)	2.8 ± 0.7	2.9 ± 0.7	3.3 ± 0.9	4.0 ± 1.0	-0.4 (-0.9, 0.0)	0.026	0.054
0-<3 months	2.8 ± 0.7	2.9 ± 0.7	3.1 ± 0.9	3.9 ± 1.0	-0.6 (-1.1, -0.1)		
3-6 months	2.8 ± 0.6	2.8 ± 0.7	3.4 ± 0.7	4.0 ± 1.0	-0.3 (-0.8, 0.1)		

Plus–minus values are means ± SD. Otherwise data are median (quartiles). Values reported to 2 significant figures.

α Baseline values were calculated with the use of data assessed by continuous glucose monitoring during the pre-randomisation run-in phase during early pregnancy. One participant was missing baseline data assessed by continuous glucose monitoring.

β The postpartum phase is from delivery until 24 weeks postpartum. Outcomes were assessed with the use of sensor data assessed by continuous glucose monitoring.

δ Based on a repeated measures linear regression model adjusting for baseline trial outcome, insulin delivery modality, and site as a random effect. Difference is hybrid closed-loop – standard care. P-values and confidence intervals adjusted using the adaptive Benjamini-Hochberg procedure.

ϕ In the HCL group, two participants had missing data in the 0-<3 months period and three had missing data in the 3-6 months period as assessed by continuous glucose monitoring. In the standard care group, two participants had missing data in the 0-<3 months period and five had missing data in the 3-6 months period as assessed by continuous glucose monitoring.

Figure 4.3 Time in target range 3.9-10.0mmol/L during the six-months postpartum

This figure shows time in range by 4-week period, and the time in range for the first 4-week period from day of delivery were 78% for HCL and 64% for standard care.

Dots are means, and the boxes are medians and quartiles. The whiskers are the 10th and 90th percentiles.

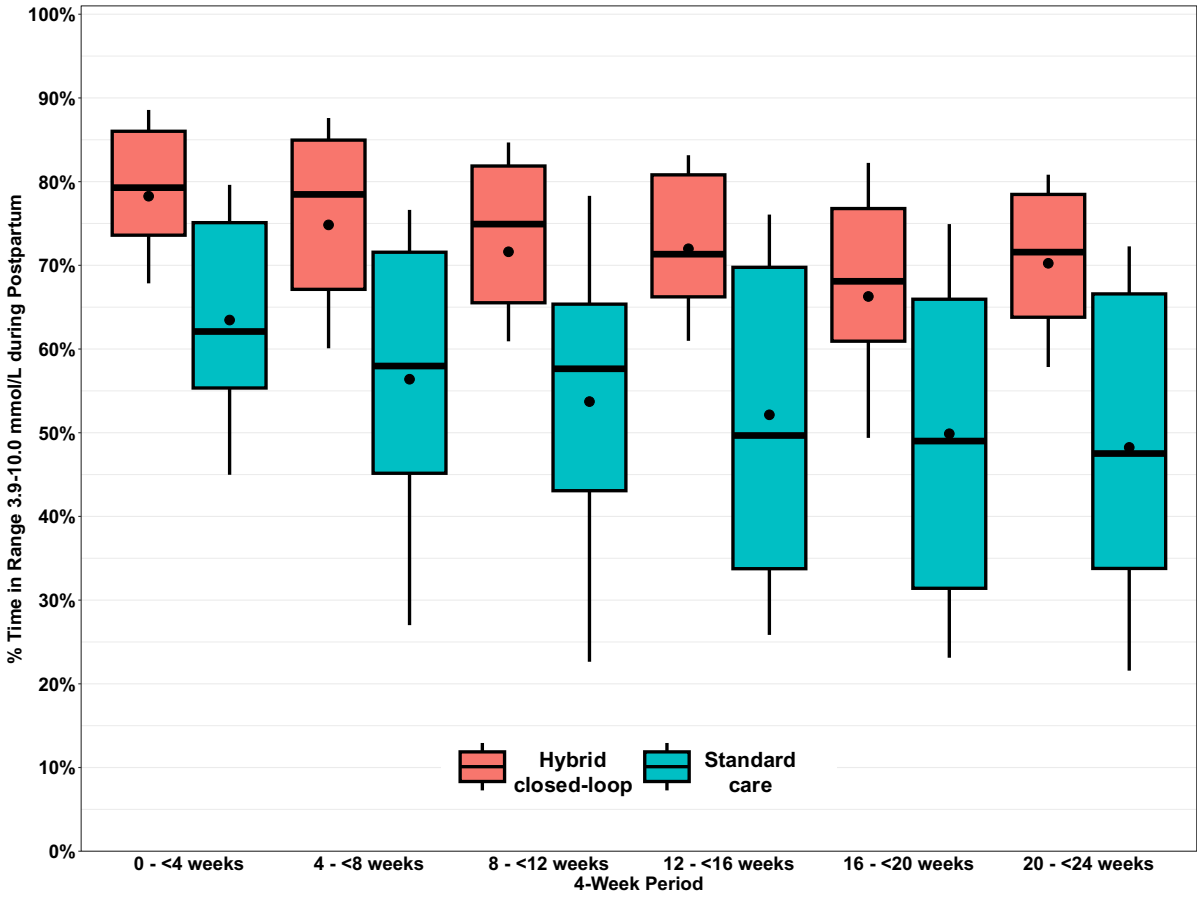


Table 4.6 Postnatal glycaemic outcomes by treatment group during first 2 weeks postpartum

Plus-minus values are mean ± SD

Outcome	Postpartum	
	Hybrid closed-loop	Standard care
Number of participants	N=26	N=27
% Time 3.9-10.0mmol/L	80% ± 9%	67% ± 14%

The between-group treatment difference appeared similar when examined separately during the first three months after delivery and 4-6 months postpartum (15% [95% CI, 7 to 23%]; 16% [95% CI, 7 to 24%]) suggesting consistency of the treatment effect across both follow-up periods. Associated glycaemic benefits of hybrid closed-loop use included lower mean glucose and less time spent above both the level 1 (10mmol/L) and level 2 (13.9mmol/L) hyperglycaemic thresholds (Table 4.5). The hybrid closed-loop group spent 15% [95% CI, -23% to -6%] less time >10.0mmol/L during the first three months after delivery with sustained reductions over 4-6 months postpartum. Likewise, the hybrid closed-loop group had lower mean glucose levels during both follow-up periods: -1.3mmol/L (-2.2 to -0.3) and -1.5mmol/L (-2.6 to -0.3) respectively. Hypoglycaemia rates were low, comparable between groups, and remained stable over the six-month follow-up period. There were temporal changes in glycaemic variability metrics consistent with higher glycaemic variation and less improvement in the standard care group at 3-6 months postpartum.

Overnight outcomes were similar to 24-hour results (Table 4.7). In the standard care group, mean overnight time in range decreased from 70 ± 14% in early pregnancy to 50 ± 19% in the first three months after delivery whereas overnight time in range was maintained in the closed-loop group from 76 ± 18% to 74 ± 11% (adjusted difference 20% [95% CI, 11 to 29%]). The overnight treatment difference was similar during the first three months and 4-6 months postpartum (19% [95% CI 11 to 27%] and 20% [95% CI 11 to 29th], respectively). This decrease in time in range was achieved by marked reductions in mean glucose and nocturnal hyperglycaemia, without differences in hypoglycaemia.

Insulin doses were consistent for each group across both time periods: 0-<3 months and 3-6 months postpartum (Table 4.8). Glycaemic outcomes were similar within hybrid closed-loop group regardless of baseline insulin modality (Table 4.9).

Table 4.7 Overnight maternal glycaemic outcomes by treatment group and 3-month postpartum period

Outcomes	RCT Baseline[α]		Postpartum[β]		Adjusted Treatment Difference[δ] (95% CI)	P-value for Treatment Effect[δ]	P-value for Interaction[δ]
	Hybrid closed-loop	Standard care	Hybrid closed-loop	Standard care			
Hours of CGM Data			1,305 ± 207	1,208 ± 337			
Number of participants[ϕ]							
0-<3 months	N=26	N=27	N=26	N=27			
3-6 months	N=25	N=24	N=25	N=24			
% Time 3.9-10.0mmol/L	75% ± 19%	70% ± 14%	76% ± 12%	54% ± 17%	19% (11%, 27%)	0.0003	0.90
0-<3 months	75% ± 19%	70% ± 14%	79% ± 12%	57% ± 16%	19% (11%, 27%)		
3-6 months	76% ± 18%	70% ± 14%	74% ± 11%	50% ± 19%	20% (11%, 29%)		
% Time 3.9-7.8mmol/L	53% ± 22%	47% ± 15%	55% ± 12%	33% ± 14%	-	-	-
0-<3 months	53% ± 22%	47% ± 15%	57% ± 13%	35% ± 13%	-		
3-6 months	54% ± 21%	47% ± 15%	53% ± 12%	31% ± 16%	-		
Mean Glucose (mmol/L)	7.9 ± 1.6	7.8 ± 1.1	8.3 ± 1.2	10.0 ± 1.9	-1.5 (-2.4, -0.6)	0.0069	0.77
0-<3 months	7.9 ± 1.6	7.8 ± 1.1	8.3 ± 1.0	9.7 ± 1.7	-1.4 (-2.3, -0.6)		
3-6 months	7.8 ± 1.6	7.9 ± 1.1	8.3 ± 1.0	10.3 ± 2.2	-1.7 (-2.7, -0.6)		
% Time >10.0mmol/L	21% ± 20%	22% ± 12%	22% ± 11%	42% ± 17%	-18% (-26%, -10%)	0.0004	0.90
0-<3 months	21% ± 20%	22% ± 12%	19% ± 12%	39% ± 17%	-18% (-26%, -10%)		
3-6 months	20% ± 19%	22% ± 13%	24% ± 11%	46% ± 20%	-19% (-28%, -10%)		
Median % Time >13.9mmol/L	2% (0%, 9%)	3% (0%, 9%)	5% (2%, 9%)	16% (7%, 27%)	-13% (-20%, -4%)	0.0069	0.29
0-<3 months	2% (0%, 9%)	3% (0%, 9%)	4% (2%, 6%)	14% (6%, 22%)	-9% (-15%, -3%)		

3-6 months	2% (0%, 8%)	3% (0%, 9%)	6% (3%, 11%)	19% (9%, 34%)	-13% (-20%, -5%)		
Median % Time <3.9mmol/L	3.4% (1.2%, 6.5%)	6.0% (1.3%, 10.1%)	1.8% (1.1%, 2.9%)	3.3% (1.5%, 5.6%)	-1.3% (-2.6%, -0.0%)	0.10	0.90
0-<3 months	3.4% (1.2%, 6.5%)	5.1% (1.3%, 10.1%)	2.0% (1.0%, 2.9%)	3.1% (1.2%, 4.6%)	-1.5% (-3.1%, 0.0%)		
3-6 months	3.2% (1.2%, 6.5%)	5.1% (1.1%, 11.5%)	1.6% (1.0%, 2.6%)	2.8% (1.2%, 5.4%)	-1.3% (-2.5%, -0.1%)		
Median % Time <3.0mmol/L	0.2% (0.0%, 0.9%)	1.0% (0.0%, 2.4%)	0.4% (0.1%, 0.6%)	0.8% (0.2%, 1.5%)	-0.4% (-0.8%, 0.1%)	0.16	0.90
0-<3 months	0.2% (0.0%, 0.9%)	1.0% (0.0%, 2.4%)	0.3% (0.1%, 0.5%)	0.6% (0.1%, 1.4%)	-0.5% (-1.1%, 0.1%)		
3-6 months	0.1% (0.0%, 0.9%)	1.0% (0.0%, 2.4%)	0.3% (0.1%, 0.5%)	0.8% (0.1%, 1.5%)	-0.4% (-0.9%, 0.0%)		
Glucose CV (%)	33% ± 9%	36% ± 9%	37% ± 5%	40% ± 6%	-1% (-4%, 2%)	0.14	0.29
0-<3 months	33% ± 9%	36% ± 9%	36% ± 6%	40% ± 7%	-3% (-6%, 1%)		
3-6 months	32% ± 9%	36% ± 9%	37% ± 5%	39% ± 7%	-0% (-3%, 3%)		
Glucose SD (mmol/L)	2.6 ± 1.0	2.9 ± 0.8	3.1 ± 0.9	4.0 ± 1.0	-0.6 (-1.1, -0.1)	0.037	0.48
0-<3 months	2.6 ± 1.0	2.9 ± 0.8	2.9 ± 1.0	3.9 ± 1.0	-0.7 (-1.3, -0.2)		
3-6 months	2.6 ± 0.9	2.9 ± 0.8	3.1 ± 0.7	4.0 ± 1.0	-0.6 (-1.1, -0.1)		

Plus–minus values are means ± SD. Otherwise data are median (quartiles).

α Baseline values were calculated with the use of data assessed by continuous glucose monitoring during the pre-randomization run-in phase during early pregnancy. One participant was missing baseline data assessed by continuous glucose monitoring.

β The postpartum phase is from delivery until 24 weeks postpartum. Outcomes were assessed with the use of sensor data assessed by continuous glucose monitoring.

δ Based on a repeated measures linear regression model adjusting for baseline trial outcome, insulin delivery modality, and site as a random effect. Difference is Closed-Loop – standard care. P-values and confidence intervals adjusted using the adaptive Benjamini-Hochberg procedure. Values reported to 2 significant figures or 4 decimal places (if small values)

ϕ In the hybrid closed-loop group, two participants had missing data in the 0-<3 months period and three had missing data in the 3-6 months period as assessed by continuous glucose monitoring. In the standard care group, two participants had missing data in the 0-<3 months period and five had missing data in the 3-6 months period as assessed by continuous glucose monitoring

Table 4.8 Insulin use and CamAPS FX system personal glucose targets

	0-<3 months		3-6 months	
	Hybrid closed-loop	**Standard care**	**Hybrid closed-loop**	**Standard care**
Total daily insulin*	N = 27	N = 27	N = 27	N = 25
Units / day Median (quartiles)	43 (38, 61)	36 (28, 45)	44 (29, 54)	40 (34, 47)
Daily basal insulin	N =27	N = 27	N =27	N =25
Units / day Median (quartiles)	28 (19, 43)	19 (16, 23)	26 (17, 38)	23 (18, 26)
Daily bolus insulin	N =27	N =23	N =27	N =23
Units / day Median (quartiles)	17 (10, 22)	20 (13, 27)	14 (11, 22)	18 (13, 24)
Personal glucose target	N = 28	-	N =28	-
mmol/L Mean ± SD	5.92 ± 0.34	-	5.89 ± 0.41	-

* In the hybrid closed-loop group, one participant was missing total daily, daily basal and daily bolus insulin data in the 0-<3months period and the 3-6 months period.
In the standard care group, two participants were missing total daily and daily basal insulin data in the 0-<3 months period and four participants in the 3-6 months period. Six participants were missing daily bolus insulin data in the 0-<3 months period and the 3-6 months period.

Table 4.9 Postnatal glycaemic outcomes by baseline insulin modality

Plus–minus values are means ± SD. Otherwise data are median (quartiles)

Outcomes	Hybrid closed-loop			Standard care		
	Pump	MDI	AID	Pump	MDI	AID
Number of participants						
0-<3 months	N=15	N=10	N=1	N=11	N=15	N=1
3-6 months	N=14	N=10	N=1	N=10	N=14	N=0
% Time 3.9-10.0mmol/L						
0-<3 months	74% ± 14%	76% ± 10%	68%	57% ± 16%	56% ± 16%	73%
3-6 months	71% ± 8%	68% ± 11%	57%	52% ± 17%	48% ± 21%	-
Mean Glucose (mmol/L)						
0-<3 months	8.3 ± 1.8	8.1 ± 1.1	8.1	9.4 ± 1.8	10.0 ± 1.9	8.3
3-6 months	8.4 ± 0.8	8.7 ± 1.2	9.7	9.9 ± 2.0	10.9 ± 2.6	-
% Time >10.0mmol/L						
0-<3 months	23% ± 14%	21% ± 11%	24%	38% ± 18%	41% ± 16%	24%
3-6 months	26% ± 8%	29% ± 12%	39%	42% ± 19%	50% ± 22%	-
Median % Time >13.9mmol/L						
0-<3 months	3% (2%, 10%)	4% (2%, 7%)	10%	13% (6%, 19%)	16% (7%, 25%)	4%
3-6 months	5% (3%, 11%)	10% (4%, 13%)	20%	18% (6%, 24%)	21% (10%, 42%)	-
Median % Time <3.9mmol/L						
0-<3 months	2.1% (1.4%, 4.3%)	2.6% (1.0%, 3.8%)	7.6%	5.0% (2.6%, 5.6%)	2.7% (1.8%, 3.1%)	2.5%
3-6 months	2.1% (1.6%, 3.7%)	2.4% (0.8%, 3.5%)	4.5%	5.4% (1.7%, 9.3%)	1.6% (1.0%, 3.4%)	-
Median % Time <3.0mmol/L						
0-<3 months	0.4% (0.2%, 0.7%)	0.4% (0.2%, 0.9%)	2.2%	1.1% (0.1%, 1.7%)	0.5% (0.2%, 1.0%)	0.4%
3-6 months	0.4% (0.3%, 0.5%)	0.4% (0.2%, 0.6%)	1.1%	1.5% (0.2%, 2.3%)	0.5% (0.1%, 0.6%)	-
Glucose CV (%)						
0-<3 months	37% ± 4%	37% ± 5%	49%	40% ± 5%	40% ± 6%	36%
3-6 months	38% ± 4%	40% ± 3%	50%	41% ± 7%	37% ± 6%	-
Glucose SD (mmol/L)						
0-<3 months	3.1 ± 1.1	3.0 ± 0.7	4.0	3.7 ± 0.7	4.1 ± 1.1	3.0
3-6 months	3.2 ± 0.6	3.5 ± 0.6	4.9	4.0 ± 0.8	4.1 ± 1.1	-

Table 4.10 Safety outcomes

	Hybrid closed-loop (N = 28)	Standard care (N = 29)
Severe hypoglycaemia		
Number of events	0	1
Participants with ≥1 event	0 (0%)	1 (3%)
Incidence per 100 person years	0.0	7.0
Hyperglycaemia with ketosis		
Number of events	0	0
Mild to moderate[α]	3	0
Severe[β]	0	1
Diabetic ketoacidosis[δ]	0	0
Participants with ≥1 event	2 (7%)	1 (3%)
Incidence of diabetic ketoacidosis per 100 person years	0.0	0.0
Serious adverse event[ϕ]		
Number of events	2	6
Hypoglycaemia	0	2
Hyperglycaemia with ketosis	0	1
Other	2	3
Participants with ≥1 event	1 (4%)	6 (21%)
Incidence per 100 person years	14.5	42.0
Device-related adverse events with HCL		
Number of events[λ]	1	0
Participants with ≥1 event	1 (4%)	0 (0%)
Incidence per 100 person years	7.0	0.0
Device-related adverse events with CGM		
Number of events	0	0
Participants with ≥1 event	0 (0%)	0 (0%)
Incidence per 100 person years	0.0	0.0

HCL = hybrid closed-loop, CGM = continuous glucose monitoring

α Mild-to-moderate events include ketosis (ketones >0.5 mmol per litre) that were treated by the participant and resolved without hospital admission.

β Severe ketosis was defined as a level of plasma ketones above 1.0 mmol per litre that resulted in hospital admission and treatment with intravenous insulin. One participant had 20 events, none of which occurred while using hybrid closed-loop therapy.

δ Diabetic ketoacidosis was defined as ketosis with acidosis that resulted in treatment with fixed-rate intravenous insulin infusion.

ϕ Serious adverse events were defined as adverse events that resulted in death, a serious deterioration in health, life-threatening illness or injury, permanent impairment, in-patient or prolonged hospitalization

λ There was 1 device-related adverse events occurring in the hybrid closed-loop group. This was due to a pump infusion set failure (kinked cannula) resulting in hyperglycaemia without ketosis.

Safety outcomes

Adverse events were similar between the two groups. There was one severe hypoglycaemia event in standard care and none in the hybrid closed-loop group. There were no diabetic ketoacidosis episodes in either group during the six-month postpartum period. The rate of adverse device events in the hybrid closed-loop group was 7 per 100 person-years, with one event related to the hybrid closed-loop system (Table 4.10). This event was due to an insulin pump infusion set failure (kinked cannula) resulting in hyperglycaemia without ketosis and resolved by replacement of the infusion set. Thus this event was related to the pump equipment rather than the hybrid closed-loop algorithm itself.

Infant feeding secondary outcomes

Exclusive breastfeeding rates were lower in the hybrid closed-loop group at hospital discharge (39% vs 52%) and at 8-12 weeks postpartum (25% vs 43%), however breastfeeding rates were similar (36% vs. 42%) at six-months postpartum (Table 4.11). Glycaemic outcomes were similar for formula and breastfeeding participants in the hybrid closed-loop group. However, women in the standard insulin therapy group, who fed their babies exclusively with breastmilk had better glycaemia as measured by percentage time in range (66% for exclusive breastfeeding vs. 45% mixed feeding and 54% exclusive formula feeding, Table 4.12).

Table 4.11 Infant feeding

	Closed-Loop	Standard Care
Feeding at time of hospital discharge after delivery		
Exclusive breastfeeding* / breast milk	11 (39%)	15 (52%)
Breast milk and formula	7 (25%)	9 (31%)
Exclusive formula feeding	10 (36%)	5 (17%)
Feeding at 8-12 weeks postnatal		
Exclusive breastfeeding* / breast milk	7 (25%)	12 (43%)
Breast milk and formula	7 (25%)	5 (18%)
Exclusive formula feeding	14 (50%)	11 (39%)
Feeding at 24 weeks postnatal		
Exclusive breastfeeding* / breast milk	10 (36%)	11 (42%)
Breast milk and formula	2 (7%)	2 (8%)
Exclusive formula feeding	16 (57%)	13 (50%)

* Exclusive breastfeeding as defined by the World Health Organization as “receiving only breast milk. No other liquids or solids are given – not even water – with the exception of oral rehydration solution, or drops/syrups of vitamins, minerals or medicines”.

Table 4.12 Postnatal glycaemic outcomes by infant feeding method

Plus-minus values are means ± SD. Otherwise data are median (quartiles).

Outcomes	Exclusive Breastfeeding		Breast Milk and Formula		Exclusive Formula feeding	
	Closed-Loop	Standard Care	Closed-Loop	Standard Care	Closed-Loop	Standard Care
Number of participants						
0-<3 months	N=7	N=11	N=5	N=5	N=14	N=11
3-6 months	N=8	N=10	N=1	N=2	N=16	N=11
% Time 3.9-10.0mmol/L						
0-<3 months	80% ± 9%	66% ± 14%	75% ± 14%	45% ± 12%	72% ± 13%	54% ± 15%
3-6 months	69% ± 11%	60% ± 16%	81%	38% ± 10%	69% ± 8%	44% ± 20%
Mean Glucose (mmol/L)						
0-<3 months	7.4 ± 0.8	8.6 ± 1.3	8.2 ± 1.4	11.0 ± 1.4	8.6 ± 1.7	10.1 ± 2.1
3-6 months	8.6 ± 1.1	9.1 ± 1.7	6.8	11.5 ± 1.1	8.6 ± 0.9	11.2 ± 2.6
% Time >10.0mmol/L						
0-<3 months	16% ± 9%	29% ± 14%	23% ± 14%	54% ± 13%	25% ± 13%	42% ± 15%
3-6 months	28% ± 11%	35% ± 17%	11%	61% ± 10%	29% ± 9%	53% ± 21%
Median % Time >13.9mmol/L						
0-<3 months	2% (1%,9%)	7% (4%, 13%)	5% (2%, 10%)	20% (20%, 25%)	5% (3%, 11%)	11% (8%, 31%)
3-6 months	9% (3%, 13%)	12% (5%, 20%)	2%	27% (20%, 35%)	9% (4%, 11%)	25% (10%, 46%)
Median % Time <3.9mmol/L						
0-<3 months	3.2% (2.5%, 7.6%)	3.9% (2.1%, 5.6%)	1.4% (1.1%, 2.6%)	1.1% (0.8%, 2.2%)	2.3% (1.6%, 3.8%)	3.0% (2.5%, 5.2%)
3-6 months	1.9% (1.0%, 4.1%)	3.9% (1.7%, 7.5%)	8.2%	0.9% (0.5%, 1.3%)	2.3% (1.7%, 3.1%)	2.0% (0.4%, 5.1%)
Median % Time <3.0mmol/L						
0-<3 months	0.5% (0.3%, 2.1%)	0.9% (0.2%, 1.6%)	0.3% (0.1%, 0.5%)	0.1% (0.1%, 0.3%)	0.4% (0.3%, 0.9%)	0.6% (0.5%, 1.2%)
3-6 months	0.3% (0.1%, 0.5%)	0.9% (0.2%, 2.0%)	1.7	0.3% (0.1%, 0.5%)	0.4% (0.3%, 0.8%)	0.5% (0.1%, 0.8%)
Glucose CV (%)						
0-<3 months	37% ± 6%	40% ± 5%	37% ± 5%	37% ± 4%	38% ± 5%	42% ± 6%
3-6 months	39% ± 5%	40% ± 6%	39%	35% ± 0%	39% ± 4%	39% ± 7%
Glucose SD (mmol/L)						
0-<3 months	2.7 ± 0.6	3.4 ± 0.8	3.1 ± 0.9	4.1 ± 0.4	3.3 ± 1.0	4.3 ± 1.1
3-6 months	3.3 ± 0.8	3.7 ± 1.0	2.6	4.0 ± 0.4	3.4 ± 0.6	4.3 ± 1.0

Women's lived experiences

In the lived experience feedback, standard care participants emphasised the challenges during the postpartum period and how this affected their diabetes management (Table 4.13). *"My glucose control during pregnancy was probably the best it had ever been, then since giving birth it's been all over the show with the new (and huge) lifestyle changes, irregular eating patterns and breastfeeding" (SC11)*.

Meanwhile, hybrid closed-loop participants focussed more on the benefits of hybrid closed-loop use (Table 4.14). *"Breastfeeding and sleepless nights were much easier to manage while on closed loop system. I had no concerns about my BG and was able to focus on my recovery and caring for a newborn" (HCL18).*

Having that mental headspace and freedom to not be thinking about my blood sugars all the time has allowed me to focus on my child and the value of that can't be underestimated" (HCL13).

Table 4.13 Participant Feedback: Standard care (standard insulin delivery with CGM) participants

Themes / Subthemes	Participant quotations
Difficulties experienced during the postpartum period	**1. Managing diabetes in the postpartum period** "For the six months following birth my diabetes control has been difficult. Having 2 children makes for a busy life & fitting in controlling diabetes takes a lot of time and effort" (SC5) **2. Labile glucose levels** "My body was and still is adjusting, it has not been the same since pregnancy and birth and my hypo awareness has definitely been left affected. I seem to drop very quick and also spike after meals lots more than before I had my baby" (SC4) **3. Hypoglycaemia** "I definitely struggled with hypos a bit in the first few weeks and this made it difficult to look after my baby and also my older child." (SC9) **4. Worry about glycaemia and glucose control** "I've been really down about how drastically my glucose control changed from pregnancy to post-natal. My glucose control during pregnancy was probably the best it had ever been, then since giving birth it's been all over the shop with the new (and huge) lifestyle changes, irregular eating patterns and breastfeeding." (SC11) **5. Breastfeeding** "I have definitely found it stressful trying to manage my sugars whilst breastfeeding and to some extent knowing my blood glucose the whole time may have actually added to this stress!!" (SC9)

Benefits of CGM	**1. Less worry, more confidence** “Still felt a massive relief knowing I had my dexcom on. Having baby And looking after baby is busiest and most tired I've ever been. I was alerted of hypos that I didnt even feel. Same as during my Pregnancy. Which could have saved my life when you think about it. All those times I could have gone too low but didnt.” (SC3) **2. Changed relationship with diabetes** “I have been on many different treatments & struggled with the management of my condition. I can safely say being able to use the Dexcom completely changed my mental relationship with diabetes as it made it so much easier to manage." (SC5) **3. Alleviating difficulties related to managing diabetes in the postpartum period** "It made managing sugars much easier, especially when I was about to feed (was easy to quickly check sugars when my baby was crying to check I was safe to feed and wouldn't hypo. It has allowed me to eat more with less stress. It has also helped build my confidence when out alone with my baby.” (SC10)
Factors that facilitated diabetes self-management and increased feeling of safety	**1. Alarms** “Alarms that are predictive with Dexcom are helpful and makes me feel safer with [my baby] when my partner is at work. When you're relying on symptoms is really hard because when I'm tired or exhausted or hungry but the alarms really help with that.” (SC17) **2. Being able to monitor more closely** “Dexcom incredibly helpful to monitor trends and act accordingly with insulin changes." (SC2) **3. Being able to share glucose data with other people** “Having this linked up to my husband and parents means it does make this easier as it is always a worry when looking after young children.” (SC4) **4. Data accessible to healthcare team** “Helped me keep an eye and also helped the new team look at them after having a seizure” (SC7) **5. Not having to test / scan** “Easy checking has taken less time so therefore more incline to check in turn keeping me safer and also my baby while in my care." (SC20) **6. Accuracy** “Compared to Libre... The only time Dexcom G6 wasn't accurate is when I fell asleep on my arm.” (SC17)
Issues with CGM	**Device issues** “I have also been quite unlucky with quite a few dodgy sensors so there have been times when I have been reading high or low when it has actually been fine” (SC9) **Skin reactions** “I found I was having some severe reactions to the Dexcom adhesive. (This started happening [during pregnancy] however progressively got much worse once [my baby] was born) therefore I required multiple breaks in my Dexcom journey. This was frustrating as I feel like I my diabetes control is much improved when able to use the Dexcom. I spoke to a nurse who works with Dexcom and was offered some different options to try with regards to the reactions however it took 6+ months to find a solution that makes wearing them much more comfortable.” (SC5)

Table 4.14 Participant Feedback: Intervention (hybrid closed-loop) participants

Themes / Subthemes	Participant quotations
Benefits of hybrid closed-loop	**1. Better glucose levels** "Amazing control with closed loop system. So pleased with my blood glucose levels the past 6 months. The closed loop system is fantastic & has eased my life significantly" (HCL19) **2. Less worry, more confidence and less mental burden** "Made me feel more secure and relaxed knowing that I am less likely to have a hypo. I also feel like it takes less of my mental energy to manage my blood sugars" (HCL7) **3. Could focus less on diabetes** "Breastfeeding and sleepless nights were much easier to manage while on closed loop system. I had no concerns about my BG and was able to focus on my recovery and caring for a newborn" (HCL18) **4. Better sleep** "I sleep much easier knowing that the closed loop system is looking after me while I sleep." (HCL14) **5. Other unexpected benefits** "My recovery from my c-section was so much smoother and easier than I ever anticipated it to be and I believe this is due to my great blood sugar control and low HBA1C. I believe if I wasn't using the loop I would not be in such good health and that would have made recovery and early motherhood much harder." (HCL13)
Factors that facilitated diabetes self-management and increased feeling of safety	**1. Alarms** "I did sometimes stop feeding baby to treat a hypo whereas last time with no alarms I did think I maybe feel hypo but I'll sort it when she's finished so that felt much safer as it would keep alarming" (HCL4) **2. Allowing the HCL to manage glucose levels independently** "I've not had to think much about my blood sugars in these early weeks as I know I can rely on the loop to take care of me. Having that mental headspace and freedom to not be thinking about my blood sugars all the time has allowed me to focus on my child and the value of that can't be underestimated" (HCL13) **3. Reduced hypoglycaemia** "I'm much more confident looking after my baby as I know that hypos and other complications have been drastically reduced thanks to this system." (HCL14) **4. Being able to share diabetes management with others** "I can be led by my baby rather than led my diabetes not having to inject at the same time and always be looking for my meter. Helps plan busy times with ease off. Now with the signal sounds triggers a response with my husband and my five year old - if it goes for a low and my son will get a snack. My husband is able to do more to help me - to help deliver boluses if he's cooking and carb counts." (HCL12)

Issues with hybrid closed-loop	**Device issues** **“**some issues with connection between pump and phone caused some unpredictable glucose levels. resolved with new pump.” (HCL18) **Second phone** “Some things easy to forget with a new baby e.g taking a second phone everywhere with you.” (HCL8)

4.6 Discussion

Women continuing hybrid closed-loop from pregnancy into the postpartum period spent 15% more time within the non-pregnancy glucose target range (3.9-10.0mmol/L), an additional 3.6 hours a day, compared to those assigned to CGM alongside standard care insulin delivery. Glycaemic improvements were achieved by a marked reduction in maternal hyperglycaemia, especially evident overnight, and without additional hypoglycaemia.

The baseline glycaemic metrics obtained during early pregnancy (prior to randomisation, at approximately 10 weeks’ gestation), were similar at 70% time in range (3.9 - 10.0mmol/L) in both groups. Women assigned to hybrid closed-loop returned to target glycaemia (70% time spent between 3.9 – 10.0mmol/L) in the immediate postpartum period, whereas women assigned to standard care alongside real-time CGM, demonstrated a marked deterioration. The hybrid closed-loop treatment benefit was apparent from the first two weeks after birth and was consistently maintained over the six-month follow-up period. The first few weeks after birth, when women experience the most profound physiological and lifestyle transitions, often coincides with limited clinical input and oversight compared to the intensive support women receive during pregnancy.

Our results differ from the smaller Canadian CLIMB and American PICLS studies which described participants with lower baseline HbA1c: 52mmol/mol and 51mmol/mol and directly compared hybrid closed-loop with standard care over shorter time-frames (10 weeks and 4-6 weeks respectively). These two studies found continued optimal glycaemia both in hybrid closed-loop and in control arm participants using open-loop insulin pump therapy: CLIMB time in range (3.9-10.0mmol/L) 79% vs. 78% and PICLS 75% vs 77%, without demonstrable clinical efficacy of hybrid closed-loop system use (197,198). Rates of hypoglycaemia were similar (~2%) among hybrid closed-loop participants between our AiDAPT trial participants and the CLIMB study but higher in the PICLS study (4.5%), most likely reflecting differences in baseline glycaemia, the CGM sensor used or both.

It is notable that CLIMB study participants commenced hybrid closed-loop use one week postpartum because of "concerns that the basal insulin modulation with the MiniMed 670/770G closed-loop system could be too strong for the first postpartum week", reflecting hybrid closed-loop algorithm differences (197). The MiniMed 670G/770G algorithm used by CLIMB participants is "strongly influenced by total daily dose of insulin used in the previous six days", whereas previous evaluations of the intrapartum and first six weeks postpartum data supported continued use of CamAPS FX during labour, delivery and after immediately following birth (88,197). The PICLS study, although examining the continuation of MiniMed 670G use from pregnancy, also stopped hybrid closed-loop Auto Mode during maternal hospital admissions for labour and delivery and resumed use three to seven days postpartum (198).

Potential limitations of these studies are their smaller sample sizes, limited statistical power to detect between group differences, delayed start of hybrid closed-loop use and shorter duration of postnatal follow-up. It is important to note that participants in both studies received an intensive schedule of postpartum follow-up visits, with monthly specialist endocrinology clinic visits and more study contacts including up to weekly remote glucose management in both. This level of intensive postpartum support is not representative of postpartum care in the UK (203).

In this study, although exclusive breastfeeding rates were initially low in the hybrid closed-loop group, they were similar in both groups by 6 months postpartum. Furthermore, rates of any breastfeeding (exclusive plus mixed) are comparable to national breastfeeding rates in the general maternity population, where prevalence of any breastfeeding is 55% at six weeks and 34% at six months postpartum (182). Several factors beyond glycaemic control that influence women's infant feeding decisions including maternal age, parity, BMI, socio-economic and educational status in addition to gestational age at birth and mode of delivery (184,204). Our study was not designed to evaluate the complex interactions between maternal glycaemia, hybrid closed-loop therapy and infant feeding choices.

Strengths of this trial include its randomised design, larger sample size compared with similar trials, generalisability of participants across a range of glycaemic categories, and inclusion of pump-naïve participants which is important for widening access to diabetes technology. Baseline characteristics of postpartum participants mirrored the overall characteristics of the main AiDAPT study which is highly representative of national

population-based data for type 1 diabetes pregnancy (139). A further strength is the continuation of the same insulin delivery modality from pregnancy into the postpartum period, thereby eliminating any transition period between modalities which could affect maternal glycaemia. In this pragmatic postpartum extension study, there were no additional visits over and above usual clinical care.

Limitations are that these postpartum results are specific to the CamAPS FX and cannot be extrapolated to other commercially available hybrid closed-loop systems. We designed this pragmatic postpartum extension study specifically not to add burden to healthcare teams in the immediate aftermath of the COVID-19 pandemic or to participants navigating life with a newborn baby. Therefore, we did not collect data including maternal weight or frequency of clinical postpartum contacts that were unavailable by maternal telephone contact. There is the possibility of measurement bias in the treatment estimates due to missing data, however, the number of participants with missing data was very low: only four out of 57 participants had missing data for all periods. Our study was not powered to examine specific hybrid closed-loop settings (insulin to carbohydrate ratios and personal glucose targets), and the sample size is inadequate for examining complex interactions between maternal glycaemia, hybrid closed-loop therapy and infant feeding, or health economic analyses which all warrant future study. Further evaluation of hybrid closed-loop therapy use during the inpatient admissions including that for labour and delivery involving 119 participants is underway and will be reported separately.

In conclusion, the AiDAPT trial established the efficacy of hybrid closed-loop therapy during type 1 diabetes pregnancy with glycaemic benefits over and above CGM with standard insulin therapy (139). Our current findings support continued use of hybrid closed-loop therapy from pregnancy into the postpartum period. Clinical benefits are sustained throughout the first six months postpartum compared to a marked deterioration in glycaemic control with CGM and standard insulin delivery. Current provision and funding of healthcare in the UK is siloed into different streams and departments. For many mothers this contributes to a sense of abandonment as they transition from team to team (maternity services to adult diabetes care or general practice) with little to no continuity of care. This postpartum continuation of CamAPS FX hybrid closed-loop use allows mothers to maintain target glycaemic control whilst navigating clinical care transitions and adjusting to life with a newborn.

Chapter 5: Discussion

In this thesis, I have examined the efficacy and safety of the CamAPS FX hybrid closed-loop system during and in the first six months after type 1 diabetes pregnancy. These studies demonstrate:

1. Clinical efficacy and safety of CamAPS FX hybrid closed-loop therapy compared with CGM and standard insulin therapy:
    - improved time in the pregnancy-specific target glucose range (3.5 – 7.8mmol/L) with reduction in time above range and no increase in time below range
    - Reduced maternal gestational weight gain
    - Reduced pregnancy hypertensive disease
2. Women's acceptability of and preference for CamAPS FX hybrid closed-loop use in pregnancy
3. Healthcare professionals' preference and belief in the benefits of hybrid closed-loop use as recommended standard of care for management of type 1 diabetes pregnancy across the NHS
4. Clinical efficacy and safety of CamAPS FX hybrid closed-loop therapy compared with standard insulin therapy for the first 6 months postpartum after delivery
    - improved time in the target range (3.9 - 10.0mmol/L) with reduction in mean glucose and time above range
    - women's acceptability of and preference for the continuation of CamAPS FX hybrid closed-loop use from pregnancy into the postpartum period

In this chapter, I present an overall discussion of my research in the wider context of further studies examining hybrid closed-loop use in pregnancy published since the AiDAPT trial results including the NHS England implementation of pregnancy-specific hybrid closed-loop use in type 1 diabetes pregnancy. In addition, whilst I have discussed strengths and limitations of each aspect of my research in the individual chapters, I will also discuss areas of further development and avenues for future research.

5.1 Considerations for hybrid-closed loop systems in pregnancy

When evaluating the use of hybrid-closed loop, in addition to its safety aspects and effects on maternal glycaemia, other pregnancy-specific considerations should be assessed. These include the adaptability to gestational changes in glucose metabolism and insulin pharmacokinetics, user acceptability and obstetric and neonatal outcomes.

Since the AiDAPT results (simultaneously presented at the EASD conference in Hamburg, Germany and published in the New England Journal of Medicine on 5th October 2023), the CamAPS FX hybrid closed-loop system remains the only system currently licensed for use in pregnancy in the UK and across 15 other countries (Ireland, France, Spain, Germany, Italy, Poland, Czech Republic, Norway, Finland, Sweden, Denmark, The Netherlands, Canada, Australia and New Zealand).

There are now further studies examining and reporting the off-label use of other commercially available hybrid closed-loop systems, with the majority using the Medtronic MiniMed 670G and 780G systems based on the Medtronic "SmartGuard" hybrid closed-loop algorithm (177,205–209). These studies varied in design, including a single patient case study, retrospective observational studies, prospective cohort studies and one adequately powered open-label randomised controlled trial (Table 5.1).

The three smaller studies: the case study from Greece and two retrospective observational studies from Italy and Slovenia examined the use of Medtronic MiniMed hybrid closed-loop systems in one, six and 21 women respectively (177,205,206). The participants had well-managed diabetes, with pre-pregnancy HbA1c of 49mmol/mol in the Greek case study, 46mmol/mol in the Italian study, and 53mmol/mol at 5 weeks' gestation in the Slovenian study. They reported achieving the International Consensus on Time in Range target of 70% time in the pregnancy-specific target range (3.5 - 7.8mmol/L) by the second trimester if not earlier (52). There were no apparent safety concerns, but with only one diabetic ketoacidosis event reported in the Slovenian study, these studies are too small to examine safety outcomes.

Table 5.1 Studies evaluating off-label use of commercially available hybrid closed-loop systems in type 1 pregnancy (published since AiDAPT trial, NEJM, October 2023)

Study	Number of participants[α]	HCL system	Timing of HCL automode initiation
Giannolulaki et al 2024 (205) Greek case study	1 HCL	Medtronic Minimed 780G	During pregnancy: 13 weeks' gestation
Fresa et al 2024 (177) Italian single centre retrospective observational study	6 HCL	Medtronic Minimed 780G	Prior to pregnancy: median 16 weeks prior (range: 2 - 40 weeks)
Munda et al 2024 (206) Slovenian single centre retrospective observational study	21 HCL	Medtronic Minimed 780G	Prior to pregnancy: 9 participants During pregnancy: 12 participants - up to 14 weeks' gestation
Benhalima et al 2024 (207) Multicentre RCT from centres across Belgium and the Netherlands	46 HCL 49 standard care	Medtronic Minimed 780G (N=46)	During pregnancy: mean gestation in intervention (HCL) arm - 10 weeks' gestation
Quirós et al 2024 (208) Spanish multicentre prospective cohort study	59 HCL 53 MDI+CGM	Medtronic Minimed 780G (N=48) Diabeloop (N=6) Tandem Control IQ (N=5)	Prior to pregnancy: 45 participants During pregnancy: 14 participants - median 16.9 weeks' gestation (IQR 13.7 to 26.1 weeks)
Perea et al 2024 (209) Spanish multicentre prospective cohort study	40 HCL 29 Medtronic Minimed 640G[β]	Medtronic Minimed 780G (N=40)	Prior to pregnancy

[α] HCL = hybrid closed-loop therapy, MDI = multiple daily injections, RCT = randomised controlled trial, IQR = interquartile range

[β]Medtronic MiniMed 640G insulin pump with predictive low glucose suspend function to suspend insulin delivery when hypoglycaemia is anticipated – not an HCL system.

5.1.1 Comparisons with the CRISTAL study

The CRISTAL (Closed-loop Insulin Delivery in Pregnant Women With Type 1 Diabetes) study randomly assigned 95 pregnant women with type 1 diabetes in a 1:1 ratio to hybrid closed-loop therapy (Medtronic MiniMed 780G system) or to standard insulin therapy (207). It included 95 women with a mean age of 30.5 ± 4.2 years and early pregnancy HbA1c 47·4 ± 7·2mmol/mol from 12 centres across Belgium and The Netherlands. This study did not demonstrate a difference in time spent in the pregnancy-specific target range (3.5 - 7.8mmol/L) between Medtronic MiniMed 780G hybrid-closed loop users and those on standard insulin therapy: 66.5 ± 10% (hybrid closed-loop) vs. 63.2 ± 12.4% (standard care), adjusted mean difference 1.88% (95% CI -0.82% to 4.59%, p = 0.17). They found that hybrid closed-loop users spent 19 minutes less time below 3.5mmol/L and an additional 24 mins more time in range overnight. However, these small differences are unlikely to be clinically beneficial for reducing obstetric and neonatal complications. There were no differences in safety outcomes with one diabetic ketoacidosis event in each group and seven versus eight severe hypoglycaemia events in the standard care and hybrid closed-loop groups respectively.

These CRISTAL maternal glycaemia findings are in stark contrast with the AiDAPT results reported in Chapter 2 (139). In AiDAPT, CamAPS FX hybrid closed-loop users spent 10.5% (95% CI 7.0 to 14%) more time between 3.5 – 7.8mmol/L or 2.5 more hours a day. When comparing the two studies, as well as the different hybrid closed-loop systems used, there were differences in the study design, study populations and control arms. Firstly in CRISTAL, the CGM outcomes were assessed using data collected over 21 days at 4 discrete time points during pregnancy: 14–17 weeks, 20–23 weeks, 26–29 weeks, and 33–36 weeks' gestation (207,210). In AiDAPT, CGM outcomes was examined using levels measured continuously from 16 weeks' gestation to delivery, providing a more comprehensive assessment of glycaemia over the entire time period (83,139).

When comparing the longitudinal change in maternal glucose outcomes across pregnancy (Figure 5.1), CamAPS FX users in AiDAPT had a statistically significant and clinically relevant early improvement with an additional 5% time in range apparent by the end of the first trimester (139). This is in contrast to Medtronic MiniMed 780G users in CRISTAL whose glucose outcomes remained relatively static until the third trimester (207).

Figure 5.1 Percentage time spent in the pregnancy-specific target glucose range

Figure A: **AiDAPT trial**

Side by side boxplots of the %time spent within the pregnancy-specific target glucose range of 3.5-7.8mmol/L for each treatment group, as measured by continuous glucose monitoring, over each 4-weekly antenatal time period from device training until delivery. Black bars denote medians and black dots denote means.

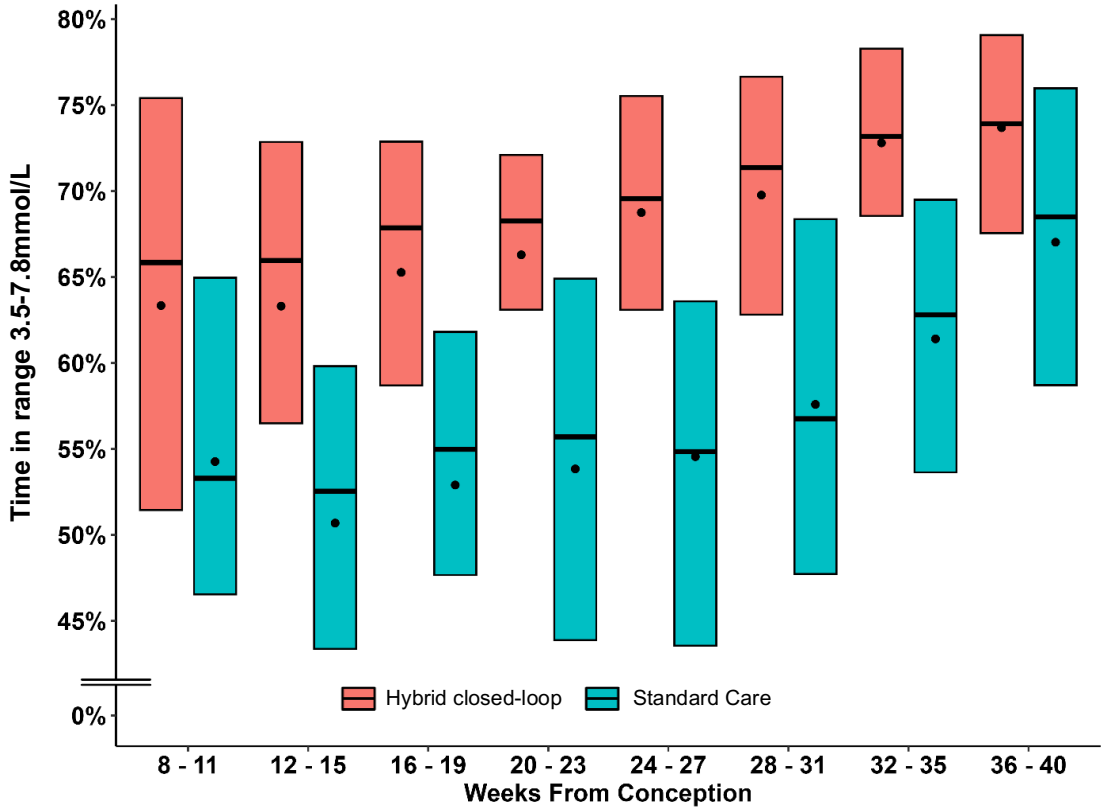
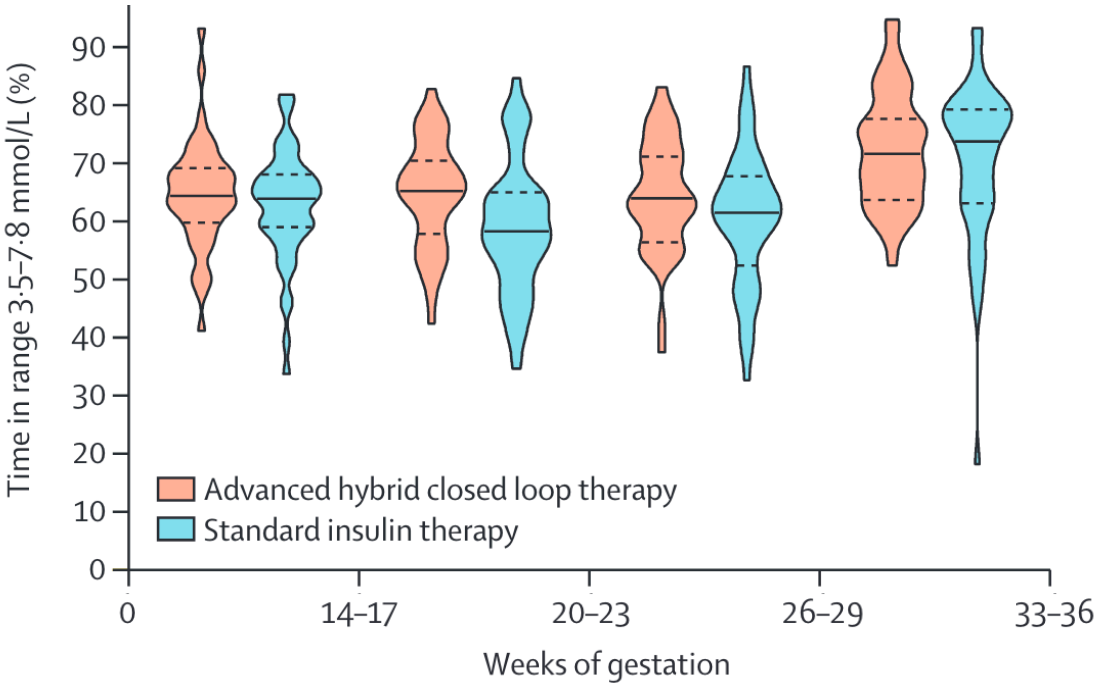


Figure B: CRISTAL study (adapted from Benhalima et al 2024) (207)

Violin plots indicate the distribution of time spent in and below the pregnancy-specific target range by treatment group at 14–17 weeks', 20–23 weeks', 26–29 weeks', and 33–36 weeks' gestation. The violin width represents the number of participants at each value. Solid lines denote medians and dotted lines denote interquartile range.



When comparing the participant characteristics, AiDAPT recruited a broader group of participants with a higher mean HbA1c at baseline, 61 ± 13mmol/mol vs. 47·4 ± 7·2mmol/mol in CRISTAL (139,207). The CRISTAL cohort included more previous pump and hybrid closed-loop users, with insulin pump therapy use at 96% in CRISTAL, compared to 48% for AiDAPT (46% standalone insulin pumps, 2% hybrid closed-loop users) participants (139,207). At recruitment in CRISTAL, 45% used hybrid closed-loop systems, and 51% used insulin pump therapy (37% with predictive low glucose suspend system, 14% standalone pumps) (139).

In CRISTAL, the majority of control arm participants continued use of this predictive low glucose suspend system (80.8%), whereas in AiDAPT only one participant opted to continue using an alternative sensor concurrently with their insulin pump (Medtronic Guarding sensor + 640G pump) in order to continue using the predictive low glucose suspend system alongside the study Dexcom G6 CGM to collect study data (139). This high rate of predictive low glucose suspend systems used in the CRISTAL control arm suggests that the Medtronic MiniMed 780G hybrid closed-loop system may not confer much additional benefit over systems that have predictive low-glucose suspend features in pregnancy.

These differences in study populations and insulin therapy, however, do not account for the difference in maternal glucose outcomes between AiDAPT and CRISTAL. CRISTAL demonstrated that in women with well managed diabetes: (early pregnancy HbA1c of 47·4 ± 7·2mmol/mol) achieved a similar time in the pregnancy-specific target range: 66·5% ± 10.0% to those in AiDAPT with higher HbA1c in early pregnancy (61 ± 13mmol/mol). Furthermore, subgroup analyses demonstrated the consistent benefit of CamAPS FX with a 10.5% improvement across all HbA1c categories for AiDAPT participants including those with an early pregnancy HbA1c of <53mmol/mol (139).

5.1.2 Further real-world data of hybrid closed-loop use in pregnancy

There have been two further prospective cohort studies from Spain examining the off-label use of commercially available hybrid closed-loop system use in pregnancy. The first compared the use of three hybrid closed-loop systems Medtronic MiniMed 780G, Tandem Control IQ, and Diabeloop to multiple daily insulin injections, and the second compared the

Medtronic MiniMed780G hybrid closed-loop system with insulin pumps with predictive low glucose suspend function (Medtronic MiniMed 640G) (208,209).
Out of 112 women included in the first study, 59 used a hybrid closed-loop system, Medtronic 780G (81.4%), Diabeloop (10.2%) and Tandem Control IQ (8.4%). Most 40/59 (76.3%) commenced hybrid closed-loop use prior to pregnancy, with the rest starting during the second trimester (median gestational age 16.9 weeks). A consecutive woman using MDI and CGM in pregnancy was selected as a comparator for each woman using hybrid closed-loop therapy. Participants had a mean age of 34.8 ± 5 years and median pre-pregnancy HbA1c of 50mmol/mol (IQR 45 – 54mmol/mol). Women in the hybrid closed-loop group had a longer diabetes duration (20.0 ± 8.7 years vs. 13.6 ± 8.7) and were more likely to have received pre-pregnancy care than those in the comparator group. There were no significant between-group differences in the mean change in HbA1c from first to third trimester or in time spent in the target range (3.5-7.8mmol/L), although hybrid closed-loop users spent less time below 3.5mmol/L. There were no diabetic ketoacidosis events in either group, and no episodes of severe hypoglycaemia in the hybrid closed-loop group with two in the comparator group.

The authors performed a subgroup analysis among women (46%) with an early pregnancy HbA1c of >48mmol/mol. There was no difference in HbA1c, and whilst more hybrid closed-loop users met the sensor glucose targets (i.e. >70% of time between 3.5-7.8mmol/L) this was only apparent during in the first trimester, further suggesting that these algorithms need additional refinement to adjust to gestational changes in glucose metabolism and insulin sensitivity during the second and third trimesters (208).

The second Spanish study recruited 69 women who were using a Medtronic MiniMed 780G hybrid closed-loop system (N=40) or Medtronic 640G, an insulin pump with predictive low glucose suspend system (N=29) from prior to pregnancy. Similar to the first Spanish study, there was no between group difference in mean change in HbA1c from first to third trimester. This was in spite of an initial difference in the first trimester time in the pregnancy-specific range (66.1 ± 10.2% in the MiniMed 780G group vs 59.0 ± 9.3% with MiniMed 640G), which did not persist into the second and third trimesters. In terms of safety outcomes, there were no events of diabetic ketoacidosis in either group and no episodes of severe

hypoglycaemia in the MiniMed 780G hybrid closed-loop group with two reported in the comparator MiniMed 640G group (209).

It is increasingly apparent that hybrid closed-loop systems are not equivalent when it comes to managing glycaemia during the second and third trimesters of pregnancy and that further algorithm adaptations may be needed for systems that were not refined for use in pregnancy.

5.1.3 Adaptability and usability of a hybrid-closed system for pregnancy

Whilst there are differences in study design and study populations between AiDAPT and the other studies, when examining the performance of the hybrid closed-loop system, the main difference will be the system's algorithm. The CamAPS FX system has been developed over the last two decades and tested in pregnancy from early on in its development through the "closed-loop systems in pregnancy" (CLIP) studies. These refined the algorithm to adapt to early and late gestations (CLIP-01), high carbohydrate meals and snacks (CLIP-01 and 2), physical activity (CLIP-02) in a controlled inpatient setting before examining continuous use in the home setting starting with overnight only (CLIP-03) before progressing to continuous 24-hour use (CLIP-04) (84–87).

There has not been the same iterative development process of the other commercially available hybrid closed-loop systems to adapt their algorithms to the specific gestational requirements of pregnancy. There is a pregnancy-specific zone model predictive controller (zone-MPC) based closed-loop control system, referred to as CLC-P in development (93–95). It has so far only been examined in the home setting, in ten women, starting from a mean gestation of 23.7 ± 3.5 weeks' gestation until delivery. However, the algorithm is still in the experimental phase and there is no control or comparator group to examine whether the reported improvement in time range of 14% is attributed to the algorithm or to clinical and gestational changes.

A randomised controlled trial examining the off-label use of the Tandem Control IQ hybrid closed-loop system in pregnancy: CIRCUIT (closed-loop insulin delivery by glucose responsive computer algorithms in type 1 diabetes pregnancies, NCT04902378) is expected to be published in 2026. However, this is also a commercially available system, which to the best of our knowledge, has not been developed with adaptations specific to pregnancy (211).

CamAPS FX has several features that help it adapt to pregnancy. The first feature is the glucose target, which is the glucose level at which the algorithm will adjust the insulin delivery to target. As CamAPS FX was developed to be adaptable to pregnancy, the personal glucose target of the system can be set as low as 4.4mmol/L with a continuous scale to match the user's requirements and insulin resistance and sensitivity. Recommended settings for pregnancy are 5.5mmol/L for the first trimester, before lowering the target glucose to 5.0mmol/L and 4.5mmol/L overnight in the second and third trimesters. This allows the system to match the increasing insulin resistance during the second and third trimesters once the hypoglycaemia risk has reduced.

A limitation of the CamAPS FX system is the current requirement of an android smartphone. Unlike other hybrid closed-loop systems where the algorithm is part of the associated insulin pump software, the CamAPS FX is a standalone smartphone application which then integrates with an insulin pump and CGM system. This restriction to android smartphones could disadvantage individuals who do not have access to a compatible smartphone.

As most studies have examined the off-label use of Medtronic MiniMed hybrid closed-loop systems, I will focus on this system for comparison with CamAPS FX. The Medtronic MiniMed hybrid closed-loop systems' automatic algorithm, "SmartGuard", has only three fixed auto basal glucose targets that can be selected: 5.5, 6.1 or 6.7mmol/L but these are all higher than the recommended pregnancy target level of 5.0mmol/L. With CamAPS FX, the user is also able to use specific features to allow the system respond to other factors that can affect maternal glycaemia including physical activity and concurrent illness by using the "boost" and "ease off" functions. In contrast, the Medtronic MiniMed interface does not have the ability to modulate the algorithm-calculated the basal rate.

Additionally, the SmartGuard algorithm also has a safety feature called "Safe Meal Bolus" where the algorithm will adjust mealtime boluses to prevent hypoglycaemia. However, when used in pregnancy, this can reduce mealtime boluses leading to subsequent postprandial hyperglycaemia and worsening glycaemia (28). In order to overcome this, healthcare professionals and patients have devised techniques primarily to input additional carbohydrates that have not been consumed (92). These are termed "fake carbs", "ghost carbs" or "assisted carbohydrate estimation" in order to administer additional correction boluses or augment mealtime boluses (177,205–207,209).

In the CRISTAL study, 61% of participants (28/46) used “fake carbs” for postprandial hyperglycaemia to assist the automated basal delivery, from 19 weeks’ gestation, however some commenced from early pregnancy (207). A major concern about using “fake carbs” is the risk for post-meal hypoglycaemia, and or the requirement for additional carbohydrate intake to mitigate against post-meal hypoglycaemia, which together with increased insulin doses (required to overcome system limitations) could contribute to the additional gestational weight gain which may increase gestational risks of hypertensive disorders including pre-eclampsia, venous thromboembolism, postpartum haemorrhage and large for gestational age birthweight (212–214).

5.1.4 Obstetric and neonatal outcomes

Unlike outside of pregnancy where the main measures of therapy efficacy are glycaemia and rates of long term diabetic complications, there are more complications associated with diabetes in pregnancy for both the mother and baby (6,8–10). Whilst studies are often not powered for these pregnancy outcomes, they are still important factors to report when evaluating therapies for diabetes in pregnancy (Table 5.2).

In the AiDAPT trial, fewer cases of gestational hypertension and pre-eclampsia were observed in the hybrid closed-loop arm (10% hybrid closed-loop vs. 32% standard care for gestational hypertension and 7% vs. 20% for pre-eclampsia). However, there were some differences in parity, with fewer multiparous women in the standard care group: 40% vs 66% in the closed-loop group (139). Women in the hybrid closed-loop group also gained less weight during pregnancy (11.1 ± 6.1kg vs. 14.1 ± 6.1kg) than those on standard insulin therapy and had lower rates of large for gestational age (>90th centile) birthweight: 39% compared to 50% in standard care. This is considerably lower than in previous CGM studies and below the UK population rate of 50% in type 1 diabetes (6). Babies in the hybrid closed-loop group, were born a mean five days earlier than the standard care group but with a larger variation in gestation (36 weeks 3 days ± 2 weeks vs. 37 weeks 1 day ± 1 week with standard care). There were no between group differences in neonatal morbidity or in rates of NICU admission, suggesting that differences in gestational age at birth were not associated with clinically important neonatal health concerns (139).

Table 5.2 Obstetric and neonatal outcomes

A. Obstetric outcomes*

Study	**Participants**[α]	**Maternal Outcomes**			
		Pre-eclampsia N (%)		**Maternal gestational weight gain** (kg)	
Lee et al 2023 (139) AiDAPT Trial (RCT)	59 HCL (CamAPS FX) 60 standard care (CGM + MDI / insulin pump)[β]	HCL 4/59 (7%)	Standard care 12/60 (20%)	HCL (N=59) 11.1 ± 6.1	Standard care (N=60) 14.1 ± 6.1
Benhalima et al 2024 (207) CRISTAL Study (RCT)	43 HCL (Medtronic MiniMed 780G) 46 standard care (MDI / insulin pump)[δ]	HCL 4/43 (9.5%)	Standard care 2/46 (4.3%)	HCL (N=43) 11.8 ± 4.2	Standard care (N=46) 13.9 ± 5.7
Quirós et al 2024 (208) Spanish multicentre prospective cohort study	59 HCL Medtronic Minimed 780G (N=48) Diabeloop (N=6) Tandem Control IQ (N=5) 53 MDI + CGM	HCL 10/56 (17.9%)	MDI + CGM 7/51 (13.7%)	HCL (N=50) 14.6 ± 5.0	MDI + CGM (N=41) 11.3 ± 5.0
Perea et al 2024 (209) Spanish multicentre prospective cohort study	40 HCL 29 Medtronic Minimed 640G[ϕ]	HCL 8/40 (20.5%)	MiniMed 640G 3/29 (10.3%)	HCL (N=40) 15.0 ± 4.9	MiniMed 640G (N=29) 13.5 ± 4.0

*Plus-minus values are means ± SD

α HCL = hybrid closed-loop therapy, MDI = multiple daily injections, CGM = continuous glucose monitor

ϕ Medtronic MiniMed 640G: insulin pump with predictive low glucose suspend function (insulin delivery is suspended when hypoglycaemia is anticipated – not an HCL system)

β 5% using alternative HCL system or Medtronic MiniMed 640G with predictive low glucose suspend function

δ 80% using Medtronic MiniMed 640G with predictive low glucose suspend function

B. Neonatal outcomes

Study	Participants[α]	Neonatal Outcomes			
		Gestational age at delivery* weeks + days		**Large for gestational age** N (%)	
AiDAPT Trial (RCT) Lee et al 2023 (139)	59 HCL (CamAPS FX) 60 standard care (CGM + MDI / insulin pump)[β]	HCL (N=59) 36+3 (± 2+0)	Standard care (N=60) 37+1 (± 1+0)	HCL 23/59 (39%)	Standard care 30/60 (50%)
CRISTAL Study (RCT) Benhalima et al 2024 (207)	43 HCL (Medtronic MiniMed 780G) 46 standard care (MDI / insulin pump)[δ]	HCL (N=43) 37+2 (± 1+1)	Standard care (N=46) 37+5 (± 1+1)	HCL 24/43 (55·8%)	Standard care 31/46 (67·4%)
Quirós et al 2024 (208)	59 HCL Medtronic Minimed 780G (N=48) Diabeloop (N=6) Tandem Control IQ (N=5) 53 MDI + CGM	HCL (N=53) 38+0 (37+0, 38+4)	MDI + CGM (N=59) 38+0 (36+5, 38+5)	HCL 40/58 (69.0%)	MDI + CGM 30/52 (57.7%)
Perea et al 2024 (209)	40 HCL 29 Medtronic Minimed 640G[ϕ]	Not reported as per treatment group: but most participants delivered at 38 weeks' gestation		HCL 29/40 (72.5%)	MiniMed 640G 11/29 (37.9%)

*Gestational age at delivery is reported in weeks + days and in the form of mean (± SD) or median (quartiles)
From Quirós et al, days are calculated as decimal multiplied by 7.
α HCL = hybrid closed-loop therapy, MDI = multiple daily injections, CGM = continuous glucose monitor
ϕ Medtronic MiniMed 640G: insulin pump with predictive low glucose suspend function (insulin delivery is suspended when hypoglycaemia is anticipated – not an HCL system)
β 5% using alternative HCL system or Medtronic MiniMed 640G with predictive low glucose suspend function
δ 80% using Medtronic MiniMed 640G with predictive low glucose suspend function

In the CRISTAL study, Medtronic MiniMed 780G hybrid closed-loop users who started pregnancy spending 60.5% time in range (3.5 – 7.8mmol/L), managed to maintain 66.5% time during pregnancy (207). Like AiDAPT, the CRISTAL study was not powered for obstetric or neonatal outcomes. The rates of gestational hypertension were slightly lower in the hybrid closed-loop group (9.3% hybrid closed-loop vs. 13.0% in standard care), but with increased pre-eclampsia rate (9.5% vs. 4.3%) among hybrid closed-loop users. This is consistent with the higher rates of pre-eclampsia observed in the hybrid closed-loop users in both Spanish cohort studies (208,209).

Maternal weight gain in CRISTAL was similar: 11.8 ± 4.2kg in the hybrid closed-loop group vs. 13.9 ± 5.7kg standard care (207). In the first Spanish study by Perea et al, pregnant women in the hybrid closed-loop group gained more weight: 14.6 ± 5.0kg vs. 11.3 ± 5.0kg, with most notable differences in those with early pregnancy HbA1c >48mmol/mol (16.3 ± 5.9kg vs. 10.9 ± 5.1kg) (208). Mean maternal gestational weight gain was also higher in hybrid closed loop users in the second Spanish study: 15.0 ± 4.9kg vs. 13.5± 4.0kg (209).

In terms of neonatal outcomes, most babies were born at 37-38 weeks' gestation in all three studies, however with more preterm births among hybrid closed-loop group women in Perea et al (25% vs 10.3%) (207–209). Large for gestational age birthweight rates were high in both groups in CRISTAL (hybrid closed-loop 56% vs 67% standard care), with higher rates among hybrid closed-loop users in both Spanish real-world studies (69 vs 58% Quirós et al, 72% vs 38% Perea et al) (207–209).

The obstetric and neonatal outcomes of these studies highlight the differences between hybrid closed-loop systems. Systems that achieve target glycaemia outside pregnancy or in select pregnant population with techniques to overcome algorithm limitations, can differentially impact rates of obstetric and neonatal complications.

5.1.5 Women's experience and acceptability of non-licensed hybrid closed-loop systems in pregnancy

Four studies have evaluated the women's experience of using the MiniMed 780G hybrid closed-loop system in one, six, 13 and 46 women respectively (99,105,205,207). Three used questionnaires with open-ended questions whilst the CRISTAL study used patient reported outcomes, namely, the Diabetes Treatment Satisfaction Questionnaire (210). Overall,

participants described subjective benefits in terms of glycaemic control and lessening of diabetes burden and mental load (99,105,207). One study, Guibert et al, asked 13 women if they would use the system again for future pregnancies and all reported that they would (105). However, others, namely Munda et al 2022 and Giannoulaki et al also captured perceived disadvantages (Figure 5.2) (99,205). Women described "difficulties with not understanding the working of the algorithm" and the inadequacy of the target range and system (99,205). One participant felt that "the pump was failing me… during the last trimester when hormonal changes were extreme" and women from both studies highlighted the "necessary tricking of the system" and use of "fake carbs": "… it takes a while to lower a high glucose result and "fake" carbs are used as a strategy, whereas with my previous system you can intervene directly and correct it." (99,205)

Table 5.3 Women's lived experience of Medtronic MiniMed 780G use in type 1 diabetes pregnancy
(adapted from Giannoulaki et al 2024) (205)

Advantages	Disadvantages
"In general, the system has done a great job during the entire pregnancy, even though it is not programmed for pregnancy."	"The only period I felt like the pump "is failing me" was during the last trimester when hormonal changes were extreme…"
"… the system is way better compared to my former regimen…"	"… it takes a while to lower a high glucose result and "fake" carbs are used as a strategy, whereas with my previous system you can intervene directly and correct it."
"… it does a great job at preventing hypoglycaemia."	

Participant conclusion and suggestion:
"Due to constant changes in insulin needs during pregnancy two factors are crucial:
1. The medical team to review my data weekly or sooner and act immediately
2. The system is able to change the basal rates within 1-2 days and not wait longer."

A study of six highly selected early-adopters of the Tandem Control IQ hybrid closed-loop system described satisfaction with the glucose control, improvement in sleep and alleviation of burden and stress. However, they also noted frustration with lack of expertise from non-specialist diabetes staff especially at the time of delivery and hospital admissions (101).

5.1.6 Not all hybrid closed-loop systems are the same

Taken together these studies of hybrid closed-loop systems demonstrate that different hybrid closed-loop systems are not the same especially during the second and third trimesters of pregnancy. The unique and challenging nature of managing glycaemia in pregnancy unmasks these differences in the algorithms and varying ability to improve outcomes in pregnancy: glycaemic, maternal, neonatal and user experiences. Data from CONCEPTT demonstrated that every 5% improvement in time spent in target range confers benefit to obstetric and neonatal outcomes (57,64). So far, only the AiDAPT trial has demonstrated this clinically relevant improvement in glycaemia over and above that achieved by standard insulin therapy by using the CamAPS FX hybrid closed-loop system. This is perhaps unsurprising given that CamAPS FX is the only hybrid closed-loop system that can set and work with a glucose target of 5.0mmol/L or lower and has other in-built features that can help the system adapt and overcome the challenges of increased day-to-day variability and gestational changes to insulin pharmacokinetics and insulin resistance. As highlighted by both women and authors of these studies more needs to be done to refine the algorithms of non-licensed hybrid closed-loop systems to better align with the pregnancy requirements and thereby improve pregnancy outcomes (99,207).

5.2 Dissemination and implementation

The main biomedical and qualitative AiDAPT results were submitted as academic in confidence data to the National Institute for Health and Clinical Excellence Diagnostics Assessment team, for the assessment of hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes and the NICE health technology appraisal for use of hybrid closed-loop therapy (TA943) was subsequently updated in December 2023 (196). In relation to pregnancy their updated recommendation was:

“Hybrid closed-loop systems are recommended as an option for managing blood glucose levels in type 1 diabetes for women, trans men and non-binary people who are pregnant or planning to become pregnant. Hybrid closed-loop systems are only recommended if they are procured at a cost-effective price agreed by the companies and NHS England and implemented following NHS England's implementation plan.”

In January 2024, the NHS England Hybrid closed loop technologies: 5-year implementation strategy was published (215). The strategy comprised of six guiding principles "to ensure access to clinically- and cost-effective technologies is provided in a fair, transparent and equitable manner." Pregnancy and planning pregnancy has been identified by the strategy as one of the areas of "greatest need" where people "are likely to benefit the most". Funding and provision of training and education for both healthcare professionals and people with diabetes are highlighted as priorities to ensure equal access to hybrid closed-loop independent of ethnicity, geography and socio-economic background, which is consistent with the main potential challenges raised by healthcare professionals in qualitative interviews, as discussed in Chapter 3 (145,215).

Roles and responsibilities of different aspects of the health service and healthcare adjacent groups are also outlined, many of which echo possible solutions suggested by healthcare professionals from the qualitative interviews. Manufacturers and suppliers are expected to negotiate discounts with NHS England to facilitate access to as many people with diabetes as possible; provide training to both NHS staff and patients and provide helplines during core working hours and an emergency specialist diabetes product support helpline 24-hours a day, 365 days a year (215).

For regional clinical teams, the implementation strategy has made available funding to support diabetes centres who take on the role of early hybrid closed-loop adopters, to provide and support training for less experienced spoke departments in their area; as well as for staff at these spoke departments to be freed up in terms of time avail of this regional training and development robust care pathways. NHS England also laid out their intention and work with professional representative bodies such as the Diabetes Technology Network to update, develop and commissioning educational resources for both staff and patients including resources in non-English languages.

Over the last year, with the emerging evidence on the performance of different hybrid closed-loop systems in pregnancy, the NHS England reimbursement guidance and updated Saving Babies' Lives Care Bundle (element 6, version 3.2) have evolved to specify the recommendation for a pregnancy specific hybrid closed-loop system which is defined by the following criteria (216):

1. Licensed for use in pregnancy
2. Has a glucose target of <5mmol/L
3. Evidence of a clinically relevant improvement in maternal glucose outcomes (> 5% increased time in the pregnancy glucose target range 3.5 - 7.8mmol/L compared to standard care with CGM and standard insulin delivery by multiple daily injections or insulin pump)

Currently, CamAPS FX is the only hybrid closed-loop system that meets these criteria and thus NHS England has ring-fenced funding available to integrated care boards to facilitate switching women who are using insulin pumps that are not compatible with CamAPS FX. To ensure equity amongst women with type 1 women and mitigate against disadvantaging women who do not already own or cannot afford a compatible android smartphone, NHS England, together with industry manufacturers and suppliers, have developed a digital essential package to supply a compatible smartphone on the NHS Supply Chain framework (further supplier information included in the Appendix). CamDiab is also in the process of developing iOS (Apple mobile operating system) compatibility for CamAPS FX which has recently launched in Sweden with a staged rollout to the UK and further countries planned.

Over the 18 months since the publication of the AiDAPT results, there has been a huge amount of progress with respect to hybrid closed-loop use and provision in the UK. It has been a privilege and joy to have been part of the dissemination of results; sharing of expertise I have gained supporting women's use of this technology in pregnancy and meeting like-minded healthcare professionals and researchers who care so much about improving outcomes for women with diabetes and their babies.

5.3 Areas of further development and future research

The AiDAPT data are having an immediate impact on the clinical care of women with type 1 diabetes before and during pregnancy, with an estimated 1000 CamAPS FX users following publication of the NICE Technology Appraisal 943, and the NHS England ring-fenced funding (April 2025). However, there are many avenues for future research to further our understanding of the different hybrid closed-loop systems and continue to improve outcomes for these women.

Health economics

One important aspect is the cost implications of hybrid closed-loop use in pregnancy. Pregnancy and diabetes-related outcomes such as hypertensive disease, prolonged maternal admissions, neonatal intensive care admissions and pregnancy loss including stillbirth and neonatal death are associated with increased costs to healthcare providers (217–220).

Previous studies into the health economics and cost effectiveness of continuous glucose monitoring from the CONCEPTT study demonstrated cost neutrality of continuous glucose monitoring in the Canadian healthcare system (57,221). In the UK setting, estimated cost savings of £9.6 million to the NHS with the routine use of continuous glucose monitoring in type 1 diabetes pregnancy was mainly attributable to reductions in number and duration of neonatal intensive care admissions (222). Given the clinical efficacy of hybrid closed-loop use and potential reduction of pregnancy complications, any increased costs of hybrid closed-loop therapy are likely to be offset by reductions in obstetric and neonatal complications.

Further understanding of different hybrid closed-loop algorithms

There are currently four commercially available hybrid closed-loop systems in the United Kingdom, each with their own algorithm. Not all individuals will want to use the CamAPS FX system which has been examined through this thesis. Observational studies support clinical observations that not all algorithms are equal when used in pregnancy (139,207). From a clinical point of view, more studies are required examining the use of other systems (such as Tandem Control IQ and Omnipod 5) in pregnancy and more specifically comparing the systems for both glycaemic and obstetric and neonatal outcome. This would really help clinicians to give us evidence-based recommendations, when women wish to continue a hybrid closed-loop system that is not currently licensed in pregnancy (as opposed to switching to a pregnancy-specific system) during pregnancy. Data from real-world populations including the National Pregnancy in Diabetes (NPID) audit will ensure results are representative of the wider type 1 diabetes population including variation in ethnicity, education and social deprivation.

Inpatient use of hybrid closed-loop during type 1 diabetes pregnancy

During the course of pregnancy, women with type 1 diabetes may require hospital admission for care. Indications for admission may be diabetes-related including hypoglycaemia,

diabetic ketoacidosis or obstetric-related including hyperemesis gravidarum, falling insulin requirements, suspected fetal compromise or placental insufficiency. Some will require glucocorticoid administration for fetal lung maturation in cases of suspected or threatened preterm delivery. Women may also be admitted for other indications such as surgical procedures during pregnancy or other medical problems not related to diabetes or their pregnancy. The NICE Diabetes in Pregnancy guidelines recommend delivery of women with type 1 diabetes "with no other complications" between 37 and 38+6 weeks gestation by induction of labour or caesarean section, both of which require hospital admission (34). If the woman does labour spontaneously before the planned delivery as above, NICE guidelines for intrapartum care for healthy women and babies, lists diabetes as a medical condition "in which there is increased risk for the woman or their baby during or short after labour, where care in an obstetric unit would be expected to reduce this" (223).

All of these indications for admission are associated with physiological or pathological stresses which can affect maternal glycaemic control. In addition to these stresses, the changes to the daily routine including hospital meals and bed rest, also affect maternal glucose levels making insulin dose adjustments all the more challenging. Furthermore, The National Pregnancy In Diabetes audit (NPID) reported high and rising rates of severe hypoglycaemia events (14% NPID) during antenatal admissions, with an additional 3% of women experiencing inpatient diabetic ketoacidosis events (6).

As hybrid closed-loop therapy becomes more widely used in the UK following the updated NICE guidance (TA943), users may wish to continue these in the inpatient setting. Current practice varies depending on the indication for admission, including admission for labour and delivery, and there is a paucity of evidence on the optimal method of glucose monitoring and insulin delivery in this specific setting. Some departments have developed local guidance and support the continued use of these technologies whilst others still recommend the use of variable rate IV insulin infusion. Concerns regarding the risks and benefits of variable rate IV insulin infusion in obstetric care settings are present both among healthcare professionals and women with diabetes (224–227). For women with diabetes, they often find use of variable rate IV insulin infusion invasive and disempowering having control over their diabetes self-management 'taken away' with insulin dosing decisions 'in the hands' of less experienced obstetric ward staff (157). Current Joint British Diabetes Societies for Inpatient Care guidance calls for a more pragmatic approach to individualise recommendations

depending on the indication for admission and clinical status of the woman (228). Preliminary studies show promise but there is an urgent need for more evidence on the safety and efficacy of continuing hybrid closed-loop systems in maternity care settings (229).

Further development in diabetes technologies for type 1 diabetes pregnancy.

The next step in the closed-loop therapy development is that of fully automated closed-loop therapy where algorithms are able to account for and manage carbohydrate intake automatically without requiring the user to announce and manually administer insulin boluses for carbohydrates taken (which is required for optimal hybrid closed-loop systems use). This is particularly valuable in individuals who find it difficult to count carbohydrates and / or struggle to remember to announce and administer insulin for carbohydrate intake. There have been preliminary studies outside of pregnancy examining the use of both single and dual hormone systems have shown promising results over the last few years, however given the particular requirements and added challenges to managing glycaemia in pregnancy as well as the additional impact on maternal and fetal health and outcomes, studies examining their adaptability and suitability for pregnancy are required (230–232).

Fetal growth in type 1 diabetes

Women with type 1 diabetes are five times more likely to have a large-for-gestational age baby (birthweight over the 90th centile for gestational age) over the background maternity population, with a rate over 50% (6,233). Large for gestational age birthweight is associated with multiple obstetric complications including obstetric anal sphincter injuries, postpartum haemorrhage, increased risk of instrumental delivery or caesarean section and preterm birth (234,235). For the neonate, it is associated with an increased risk of respiratory distress, neonatal hypoglycaemia and neonatal intensive care admissions (235,236). In some cases, there are difficulties delivering the shoulders (shoulder dystocia) at vaginal delivery that can result in nerve injury, fractures and hypoxic brain injury (237). Furthermore, large for gestational age predisposes the infant to future obesity, type 2 diabetes and cardiovascular disease (238,239).

Numerous studies confirm the association between hyperglycaemia and risk of large for gestational age birthweight, making hyperglycaemia the key modifiable risk factor for pregnancy complications. Data from CGM studies have provided preliminary insights into the relationship between maternal glycaemia and fetal growth (240). There may be particular

gestations of fetal or placental development (e.g. 8-16 weeks, 20-28 or 28-36 weeks) more susceptible to hyperglycaemia. If particular patterns of diurnal or nocturnal glycaemic excursions contribute more to the pathophysiology of large for gestational age, this could inform more precise insulin delivery targets with the aim of reducing large for gestational age birthweight, and its associated adverse outcomes. With the rich and detailed glucose dataset from AiDAPT, there is an opportunity to further explore these patterns and further our understanding of fetal growth.

Type 2 diabetes in pregnancy

Over the last 20 years since it was highlighted by the Confidential Enquiry into Maternal and Child Health (CEMACH), diabetes in pregnancy has been a priority within diabetes and obstetric medicine. However, whilst care and outcomes has recently been improving, associated with CGM use among those with type 1 diabetes, there has been an increase in prevalence without the same improvement for mothers and women with type 2 diabetes (6). It is increasingly clear that the two populations (and the diseases themselves) are very different. People living with type 2 diabetes, especially early onset-type 2 diabetes: type 2 diabetes diagnosed before 40 years of age, have a higher risk of microvascular complications, cardiac co-morbidity and death (241–244). In the pregnancy population, there are higher rates of stillbirth, neonatal death and small for gestational age birthweight (<10th percentile for gestational age), despite apparently "better" glycaemia compared to women with type 1 diabetes, which suggests that these poor outcomes may not be solely attributable to maternal glycaemia (6). Furthermore, women with early onset-type 2 diabetes are more likely to be from non-White ethnic minorities and come from more deprived socio-economic backgrounds which are independently associated with stillbirth and poor obstetric and neonatal outcomes (6,245). Following the advances in care and good quality evidence for type 1 diabetes in pregnancy, there is a real need for a shift of perspective and focus on these women with type 2 diabetes in pregnancy in their own right rather than an extrapolation of conclusions based on a different population of women with different underlying pathophysiology.

In February 2024, the PROTECT (PRegnancy Outcomes using continuous glucose monitoring TEChnology in pregnant women with Type 2 diabetes) commenced study registration number ISRCTN12804317: https://www.isrctn.com/ISRCTN12804317. It is a multicentre, randomised controlled trial examining the clinical- and cost-effectiveness of

continuous glucose monitoring in type 2 pregnancies. Through this study, we plan to collect and analyse a large dataset of continuous glucose data from pregnant women with type 2 diabetes. We may finally start to develop evidence-based guidance on what glucose targets they should be aiming for and whether hybrid or fully closed-loop systems could also help to better manage type 2 diabetes during pregnancy and improve obstetric and neonatal outcomes.

Personal future research

I have now resumed NHS speciality training in obstetrics and gynaecology, but I am continuing to pursue my diabetes pregnancy technology research interests as a co-applicant in the PROTECT study. Through the rich AiDAPT dataset, I have been able to collect both fetal biometry and hospital admission data in order to further analyse the fetal growth trajectories and maternal inpatient admissions. These will provide further insights and improve our understanding of how women's use of hybrid closed-loop technology affects intra-uterine fetal growth and maternal glucose levels during antenatal hospital admissions in type 1 diabetes pregnancy. Through my ongoing research work, I am delivering the PROTECT study aiming to give more answers about the use of continuous glucose monitoring to an ethnically and socio-economically diverse range of pregnant women with type 2 diabetes.

References

1. Office for National Statistics. Births in England and Wales: 2022 (Refreshed Populations) [Internet]. 2024 Feb [cited 2024 Nov 7]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2022refreshedpopulations

2. Northern Ireland Statistics and Research Agency. Registrar General Northern Ireland Annual Report 2022 [Internet]. 2023 Oct [cited 2024 Nov 7]. Available from: https://www.nisra.gov.uk/publications/registrar-general-annual-report-2022

3. National Records of Scotland. Vital Events Reference Tables 2022, Annual births, deaths, marriages and other vital events [Internet]. 2023 July [cited 2024 Nov 7]. Available from: https://www.nrscotland.gov.uk/files//statistics/vital-events-ref-tables/2022/vital-events-ref-tables-22-publication.pdf

4. National Pregnancy in Diabetes Audit. NPID detailed analysis 2021 and 2022 [Internet]. 2023 [cited 2024 Nov 7]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/2022

5. The Lancet. Gestational diabetes in England: cause for concern. The Lancet. 2019 Mar 30;393(10178):1262.

6. Murphy HR, Howgate C, O'Keefe J, Myers J, Morgan M, Coleman MA, et al. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. The Lancet Diabetes & Endocrinology. 2021 Mar;9(3):153–64.

7. Gribble KD, Bewley S, Bartick MC, Mathisen R, Walker S, Gamble J, et al. Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. Front Glob Womens Health. 2022 Feb 7;3:818856.

8. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ. 2004 Apr 17;328(7445):915.

9. Persson M, Norman M, Hanson U. Obstetric and Perinatal Outcomes in Type 1 Diabetic Pregnancies. Diabetes Care. 2009 Nov;32(11):2005–9.

10. Macintosh MCM, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006 July 22;333(7560):177.

11. Murphy HR, Roland JM, Skinner TC, Simmons D, Gurnell E, Morrish NJ, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. Diabetes Care. 2010 Dec;33(12):2514–20.

12. Maresh MJA, Holmes VA, Patterson CC, Young IS, Pearson DWM, Walker JD, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. Diabetes Care. 2015 Jan;38(1):34–42.

13. Evers IM, ter Braak EWMT, de Valk HW, van der Schoot B, Janssen N, Visser GHA. Risk Indicators Predictive for Severe Hypoglycemia During the First Trimester of Type 1 Diabetic Pregnancy. Diabetes Care. 2002 Mar 1;25(3):554–9.

14. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER. Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. Diabetes Care. 2008 Jan;31(1):9–14.

15. Skajaa GØ, Fuglsang J, Kampmann U, Ovesen PG. Parity Increases Insulin Requirements in Pregnant Women With Type 1 Diabetes. J Clin Endocrinol Metab. 2018 June 1;103(6):2302–8.

16. Rayburn W, Piehl E, Lewis E, Schork A, Sereika S, Zabrensky K. Changes in insulin therapy during pregnancy. Am J Perinatol. 1985 Oct;2(4):271–5.

17. Murphy HR, Rayman G, Duffield K, Lewis KS, Kelly S, Johal B, et al. Changes in the Glycemic Profiles of Women With Type 1 and Type 2 Diabetes During Pregnancy. Diabetes Care. 2007 Nov 1;30(11):2785–91.

18. García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. Diabetologia. 2010 Mar;53(3):446–51.

19. Steel JM, Johnstone FD, Hume R, Mao JH. Insulin requirements during pregnancy in women with type I diabetes. Obstet Gynecol. 1994 Feb;83(2):253–8.

20. Powe CE, Huston Presley LP, Locascio JJ, Catalano PM. Augmented insulin secretory response in early pregnancy. Diabetologia. 2019 Aug;62(8):1445–52.

21. Jovanovic L, Knopp RH, Brown Z, Conley MR, Park E, Mills JL, et al. Declining Insulin Requirement in the Late First Trimester of Diabetic Pregnancy. Diabetes Care. 2001 July 1;24(7):1130–6.

22. Kalkhoff RK, Kissebah AH, Kim HJ. Carbohydrate and lipid metabolism during normal pregnancy: relationship to gestational hormone action. Semin Perinatol. 1978 Oct;2(4):291–307.

23. Ryan EA, Enns L. Role of gestational hormones in the induction of insulin resistance. J Clin Endocrinol Metab. 1988 Aug;67(2):341–7.

24. Friedman JE, Ishizuka T, Shao J, Huston L, Highman T, Catalano P. Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes. Diabetes. 1999 Sept;48(9):1807–14.

25. Kirwan JP, Hauguel-De Mouzon S, Lepercq J, Challier JC, Huston-Presley L, Friedman JE, et al. TNF-α Is a Predictor of Insulin Resistance in Human Pregnancy. Diabetes. 2002 July 1;51(7):2207–13.

26. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007 July;30 Suppl 2:S112-119.

27. Kerssen A, de Valk HW, Visser GHA. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous

Glucose Monitoring System. BJOG: An International Journal of Obstetrics & Gynaecology. 2004;111(9):919–24.

28. Murphy HR, Elleri D, Allen JM, Harris J, Simmons D, Rayman G, et al. Pathophysiology of postprandial hyperglycaemia in women with type 1 diabetes during pregnancy. Diabetologia. 2012 Feb;55(2):282–93.

29. Goudie RJB, Lunn D, Hovorka R, Murphy HR. Pharmacokinetics of Insulin Aspart in Pregnant Women With Type 1 Diabetes: Every Day Is Different: Table 1. Dia Care. 2014 June;37(6):e121–2.

30. Singh H, Murphy HR, Hendrieckx C, Ritterband L, Speight J. The Challenges and Future Considerations Regarding Pregnancy-related Outcomes in Women with Pre-Existing Diabetes. Curr Diab Rep. 2013 Dec;13(6):10.1007/s11892-013-0417–5.

31. Dahlberg H, Berg M. The lived experiences of healthcare during pregnancy, birth, and three months after in women with type 1 diabetes mellitus. Int J Qual Stud Health Well-being. 2020 Dec;15(1):1698496.

32. James Lind Alliance. James Lind Alliance Guidebook version 10 [Internet]. 2021. Available from: https://www.jla.nihr.ac.uk/jla-guidebook/downloads/JLA-Guidebook-Version-10-March-2021.pdf

33. Ayman G, Strachan JA, McLennan N, Malouf R, Lowe-Zinola J, Magdi F, et al. The top 10 research priorities in diabetes and pregnancy according to women, support networks and healthcare professionals. Diabet Med [Internet]. 2021 May 6 [cited 2021 May 11]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/dme.14588

34. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline [Internet]. 2020; Available from: https://www.nice.org.uk/guidance/ng3

35. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, et al. HbA1c Levels Are Significantly Lower in Early and Late Pregnancy. Diabetes Care. 2004 May 1;27(5):1200–1.

36. Herranz L, Saez-de-Ibarra L, Grande C, Pallardo LF. Non-Glycemic-Dependent Reduction of Late Pregnancy A1C Levels in Women With Type 1 Diabetes. Diabetes Care. 2007 June 1;30(6):1579–80.

37. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, et al. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: The diabetes in early pregnancy study. Metabolism. 1998 Sept;47(9):1140–4.

38. Lurie S, Danon D. Life span of erythrocytes in late pregnancy. Obstet Gynecol. 1992 July;80(1):123–6.

39. Lurie S. Age distribution of erythrocyte population in late pregnancy. Gynecol Obstet Invest. 1990;30(3):147–9.

40. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care. 2003 Jan;26(1):163–7.

41. Facchinetti A. Continuous Glucose Monitoring Sensors: Past, Present and Future Algorithmic Challenges. Sensors (Basel). 2016 Dec 9;16(12):E2093.

42. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464–76.

43. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Hirsch IB, Laffel L, Tamborlane WV, Bode BW, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009 Aug;32(8):1378–83.

44. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011 Apr;34(4):795–800.

45. Battelino T, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia. 2012 Dec;55(12):3155–62.

46. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med. 2010 July 22;363(4):311–20.

47. O'Connell MA, Donath S, O'Neal DN, Colman PG, Ambler GR, Jones TW, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia. 2009 July;52(7):1250–7.

48. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA. 2017 Jan 24;317(4):371.

49. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA. 2017 Jan 24;317(4):379.

50. Ehrhardt N, Al Zaghal E. Continuous Glucose Monitoring As a Behavior Modification Tool. Clin Diabetes. 2020 Apr;38(2):126–31.

51. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017 Dec 1;40(12):1631–40.

52. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Dia Care. 2019 Aug;42(8):1593–603.

53. Xing D, Kollman C, Beck RW, Tamborlane WV, Laffel L, Buckingham BA, et al. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther. 2011 Mar;13(3):351–8.

54. Riddlesworth TD, Beck RW, Gal RL, Connor CG, Bergenstal RM, Lee S, et al. Optimal Sampling Duration for Continuous Glucose Monitoring to Determine Long-Term Glycemic Control. Diabetes Technol Ther. 2018 Apr;20(4):314–6.

55. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. Diabetes Care. 2018 Nov;41(11):2275–80.

56. Feig DS, Asztalos E, Corcoy R, Leiva AD, Donovan L, Hod M, et al. CONCEPTT: Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial: A multi-center, multi-national, randomized controlled trial - Study protocol. BMC Pregnancy Childbirth. 2016 Dec;16(1):1–8.

57. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. The Lancet. 2017 Nov 25;390(10110):2347–59.

58. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ. 2008 Sept 25;337:a1680.

59. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care. 2013 July;36(7):1877–83.

60. Law GR, Gilthorpe MS, Secher AL, Temple R, Bilous R, Mathiesen ER, et al. Translating HbA1c measurements into estimated average glucose values in pregnant women with diabetes. Diabetologia. 2017 Apr;60(4):618–24.

61. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C Assay Into Estimated Average Glucose Values. Diabetes Care. 2008 Aug 1;31(8):1473–8.

62. Kristensen K, Ögge LE, Sengpiel V, Kjölhede K, Dotevall A, Elfvin A, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia. 2019 July;62(7):1143–53.

63. Meek CL, Tundidor D, Feig DS, Yamamoto JM, Scott EM, Ma D, et al. Novel biochemical markers of glycemia to predict pregnancy outcomes in women with type 1 diabetes. Diabetes Care. 2021 Feb 19;44(3):681–9.

64. Murphy HR. Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. 2019;6.

65. Pickup JC. Insulin-Pump Therapy for Type 1 Diabetes Mellitus. The New England Journal of Medicine. 2012;9.

66. Ranasinghe PD, Maruthur NM, Nicholson WK, Yeh HC, Brown T, Suh Y, et al. Comparative Effectiveness of Continuous Subcutaneous Insulin Infusion Using Insulin Analogs and Multiple Daily Injections in Pregnant Women with Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Womens Health (Larchmt). 2015 Mar 1;24(3):237–49.

67. Farrar D, Tuffnell DJ, West J, West HM. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database Syst Rev. 2016 June 7;2016(6):CD005542.

68. Feig DS, Corcoy R, Donovan LE, Murphy KE, Barrett JFR, Sanchez JJ, et al. Pumps or Multiple Daily Injections in Pregnancy Involving Type 1 Diabetes: A Prespecified Analysis of the CONCEPTT Randomized Trial. Dia Care. 2018 Dec;41(12):2471–9.

69. Scott EM, Feig DS, Murphy HR, Law GR. Continuous Glucose Monitoring in Pregnancy: Importance of Analyzing Temporal Profiles to Understand Clinical Outcomes. Dia Care. 2020 June;43(6):1178–84.

70. O'Malley G, Ozaslan B, Levy CJ, Castorino K, Desjardins D, Levister C, et al. Longitudinal Observation of Insulin Use and Glucose Sensor Metrics in Pregnant Women with Type 1 Diabetes Using Continuous Glucose Monitors and Insulin Pumps: The LOIS-P Study. Diabetes Technol Ther. 2021 Dec;23(12):807–17.

71. Tundidor D, Meek CL, Yamamoto J, Martínez-Bru C, Gich I, Feig DS, et al. Continuous Glucose Monitoring Time-in-Range and HbA1c Targets in Pregnant Women with Type 1 Diabetes. Diabetes Technology & Therapeutics. 2021 Oct 1;23(10):710–4.

72. Boughton CK, Hovorka R. New closed-loop insulin systems. Diabetologia. 2021 May 1;64(5):1007–15.

73. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al. Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia. N Engl J Med. 2013 July 18;369(3):224–32.

74. Forlenza GP, Li Z, Buckingham BA, Pinsker JE, Cengiz E, Wadwa RP, et al. Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial. Diabetes Care. 2018 Oct 1;41(10):2155–61.

75. Boughton CK, Hovorka R. Is an artificial pancreas (closed-loop system) for Type 1 diabetes effective? Diabet Med. 2019;36(3):279–86.

76. Dowling L, Wilmot EG, Choudhary P. Do-it-yourself closed-loop systems for people living with type 1 diabetes. Diabetic Medicine. 2020;37(12):1977–80.

77. Kesavadev J, Srinivasan S, Saboo B, Krishna B M, Krishnan G. The Do-It-Yourself Artificial Pancreas: A Comprehensive Review. Diabetes Ther. 2020 June;11(6):1217–35.

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

79. Peacock S, Frizelle I, Hussain S. A Systematic Review of Commercial Hybrid Closed-Loop Automated Insulin Delivery Systems. Diabetes Ther. 2023 May;14(5):839–55.

80. Franceschi R, Mozzillo E, Di Candia F, Maines E, Leonardi L, Girardi M, et al. A systematic review on the impact of commercially available hybrid closed loop systems on psychological outcomes in youths with type 1 diabetes and their parents. Diabetic Medicine. 2023;40(9):e15099.

81. Michou P, Gkiourtzis N, Christoforidis A, Kotanidou EP, Galli-Tsinopoulou A. The efficacy of automated insulin delivery systems in children and adolescents with type 1 diabetes Mellitus: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2023 May;199:110678.

82. Di Molfetta S, Di Gioia L, Caruso I, Cignarelli A, Green SC, Natale P, et al. Efficacy and Safety of Different Hybrid Closed Loop Systems for Automated Insulin Delivery in People With Type 1 Diabetes: A Systematic Review and Network Meta-Analysis. Diabetes Metab Res Rev. 2024 Sept;40(6):e3842.

83. Lee TTM, Collett C, Man MS, Hammond M, Shepstone L, Hartnell S, et al. AiDAPT: automated insulin delivery amongst pregnant women with type 1 diabetes: a multicentre randomized controlled trial – study protocol. BMC Pregnancy Childbirth. 2022 Dec;22(1):282.

84. Murphy HR, Elleri D, Allen JM, Harris J, Simmons D, Rayman G, et al. Closed-Loop Insulin Delivery During Pregnancy Complicated by Type 1 Diabetes. Diabetes Care. 2011 Feb;34(2):406–11.

85. Murphy HR, Kumareswaran K, Elleri D, Allen JM, Caldwell K, Biagioni M, et al. Safety and Efficacy of 24-h Closed-Loop Insulin Delivery in Well-Controlled Pregnant Women With Type 1 Diabetes. Diabetes Care. 2011 Dec;34(12):2527–9.

86. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. N Engl J Med. 2016 Aug 18;375(7):644–54.

87. Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, et al. Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial. Diabetes Care. 2018 July;41(7):1391–9.

88. Stewart ZA, Yamamoto JM, Wilinska ME, Hartnell S, Farrington C, Hovorka R, et al. Adaptability of Closed Loop During Labor, Delivery, and Postpartum: A Secondary Analysis of Data from Two Randomized Crossover Trials in Type 1 Diabetes Pregnancy. Diabetes Technology & Therapeutics. 2018 July;20(7):501–5.

89. Mathiesen ER, Alibegovic AC, Corcoy R, Dunne F, Feig DS, Hod M, et al. Insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): an open-label, multinational, randomised, controlled, non-inferiority trial. Lancet Diabetes Endocrinol. 2023 Feb;11(2):86–95.

90. Ringholm L, Pedersen-Bjergaard U, Thorsteinsson B, Damm P, Mathiesen ER. Hypoglycaemia during pregnancy in women with Type 1 diabetes. Diabet Med. 2012 May;29(5):558–66.

91. Phillip M, Nimri R, Bergenstal RM, Barnard-Kelly K, Danne T, Hovorka R, et al. Consensus Recommendations for the Use of Automated Insulin Delivery Technologies in Clinical Practice. Endocrine Reviews. 2023 Apr 1;44(2):254–80.

92. Szmuilowicz ED, Levy CJ, Buschur EO, Polsky S. Expert Guidance on Off-Label Use of Hybrid Closed-Loop Therapy in Pregnancies Complicated by Diabetes. Diabetes Technology & Therapeutics. 2023 May 1;25(5):363–73.

93. Ozaslan B, Deshpande S, Doyle FJ, Dassau E. Zone-MPC Automated Insulin Delivery Algorithm Tuned for Pregnancy Complicated by Type 1 Diabetes. Front Endocrinol. 2022 Mar 22;12:768639.

94. Ozaslan B, Levy CJ, Kudva YC, Pinsker JE, O'Malley G, Kaur RJ, et al. Feasibility of Closed-Loop Insulin Delivery with a Pregnancy-Specific Zone Model Predictive Control Algorithm. Diabetes Technology & Therapeutics. 2022 July 1;24(7):471–80.

95. Levy CJ, Kudva YC, Ozaslan B, Castorino K, O'Malley G, Kaur RJ, et al. At-Home Use of a Pregnancy-Specific Zone-MPC Closed-Loop System for Pregnancies Complicated by Type 1 Diabetes: A Single-Arm, Observational Multicenter Study. Diabetes Care. 2023 July 1;46(7):1425–31.

96. Polsky S, Akturk HK. Case series of a hybrid closed-loop system used in pregnancies in clinical practice. Diabetes/Metabolism Research and Reviews. 2020;36(3):e3248.

97. Guzmán Gómez GE, Viggiano JA, Silva-De Las Salas A, Martínez V, Urbano Bonilla MA. The Closed-Loop System Improved the Control of a Pregnant Patient with Type 1 Diabetes Mellitus. Case Rep Endocrinol. 2021 Sept 21;2021:7310176.

98. Moreno-Fernández J, García-Seco JA. Commercialized Hybrid Closed-Loop System (Minimed Medtronic 670G) Results During Pregnancy. AACE Clinical Case Reports. 2021 May;7(3):177–9.

99. Munda A, Kovacic C, Pongrac Barlovic D. Carbohydrate Intake and Closed-Loop Insulin Delivery System during Two Subsequent Pregnancies in Type 1 Diabetes. Metabolites. 2022 Nov 18;12(11):1137.

100. Vambergue A, Lemaitre M, Desir C, Le Roux Mallouf T, Tourki Y, Franc S, et al. Management of Pregnancy in a Patient with Type 1 Diabetes and Hypoglycemia Unawareness by DBL-hu Closed-Loop Insulin Delivery System. Diabetes Technology & Therapeutics. 2022 Sept;24(9):672–4.

101. Wang XS, Dunlop AD, McKeen JA, Feig DS, Donovan LE. Real-world use of Control-IQ^{TM} technology automated insulin delivery in pregnancy: A case series with qualitative interviews. Diabet Med. 2023 June;40(6):e15086.

102. Albert L, Romero A, Capel I, Cano A, Subías D, Casamitjana L, et al. Off-label use of an automated insulin delivery system in pregnant women with type 1 diabetes. Diabetes Research and Clinical Practice. 2023 Aug;202:110800.

103. Dodesini AR, Borella ND, Lepore G, Bonfadini S, Corsi A, Scaranna C, et al. Real-World Insulin Treatment in Pregnant Women with Type 1 Diabetes Using an Advanced Hybrid Closed-Loop System. Diabetes Technology & Therapeutics. 2023 July;25(7):516–8.

104. Baagar KA, Ali H, Al-Mohanadi D, Mohamud KM, Alnaimi NS, Alsharkawy N, et al. Successful use of MiniMed 780G during pregnancy. Journal of Clinical and Translational Endocrinology: Case Reports. 2023 Dec 1;30:100156.

105. Guibert C, Amoura L, Rakotoarisoa L, Plat F, Sonnet E, Lablanche S, et al. MiniMed TM 780G Advanced Hybrid Closed-Loop System Study in Pregnant Women with Type 1 Diabetes. Diabetes Technology & Therapeutics. 2023 Dec 1;25(12):893–901.

106. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ. 1998 Mar 7;316(7133):736–41.

107. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care. 2005 Mar;28(3):626–31.

108. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of Hypoglycemia: Quantification, Validation, and Utilization. Diabetes Care. 1987 Sept 1;10(5):617–21.

109. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989 May;28(2):193–213.

110. Weissberg-Benchell J, Hood K, Laffel L, Heinemann L, Ball D, Kowalski A, et al. Toward Development of Psychosocial Measures for Automated Insulin Delivery. J Diabetes Sci Technol. 2016 May;10(3):799–801.

111. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med. 2017 Oct 5;377(14):1391–8.

112. The Editors. Striving for Diversity in Research Studies. New England Journal of Medicine. 2021 Oct 7;385(15):1429–30.

113. National Pregnancy in Diabetes Audit. National Pregnancy in Diabetes Audit Report 2020 [Internet]. 2021 Oct [cited 2025 Apr 26]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/2019-and-2020

114. Ware J, Allen JM, Boughton CK, Wilinska ME, Hartnell S, Thankamony A, et al. Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes. N Engl J Med. 2022 Jan 20;386(3):209–19.

115. Boughton CK, Allen JM, Ware J, Wilinska ME, Hartnell S, Thankamony A, et al. Closed-Loop Therapy and Preservation of C-Peptide Secretion in Type 1 Diabetes. N Engl J Med. 2022 Sept 8;387(10):882–93.

116. Stenhouse E, Letherby G. Mother/daughter relationships during pregnancy and the transition to motherhood of women with pre-existing diabetes: raising some issues. Midwifery. 2011 Apr;27(2):120–4.

117. Fisher L, Gonzalez JS, Polonsky WH. The confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision. Diabet Med. 2014 July;31(7):764–72.

118. Berg M, Honkasalo ML. Pregnancy and diabetes--a hermeneutic phenomenological study of women's experiences. J Psychosom Obstet Gynaecol. 2000 Mar;21(1):39–48.

119. Berg M. Pregnancy and Diabetes: How Women Handle the Challenges. J Perinat Educ. 2005;14(3):23–32.

120. Lavender T, Platt MJ, Tsekiri E, Casson I, Byrom S, Baker L, et al. Women's perceptions of being pregnant and having pregestational diabetes. Midwifery. 2010 Dec;26(6):589–95.

121. Stenhouse E, Letherby G, Stephen N. Women with pre-existing diabetes and their experiences of maternity care services. Midwifery. 2013 Feb;29(2):148–53.

122. Tschirhart H, Landeen J, Yost J, Nerenberg KA, Sherifali D. Perceptions of diabetes distress during pregnancy in women with type 1 and type 2 diabetes: a qualitative interpretive description study. BMC Pregnancy and Childbirth. 2024 Apr 3;24(1):232.

123. Berg M, Sparud-Lundin C. Experiences of professional support during pregnancy and childbirth – a qualitative study of women with type 1 diabetes. BMC Pregnancy Childbirth. 2009 July 3;9:27.

124. Langer N, Langer O. Comparison of pregnancy mood profiles in gestational diabetes and preexisting diabetes. Diabetes Educ. 2000;26(4):667–72.

125. King R, Wellard S. Juggling type 1 diabetes and pregnancy in rural Australia. Midwifery. 2009 Apr;25(2):126–33.

126. Rasmussen B, Hendrieckx C, Clarke B, Botti M, Dunning T, Jenkins A, et al. Psychosocial issues of women with type 1 diabetes transitioning to motherhood: a structured literature review. BMC Pregnancy and Childbirth. 2013 Nov 23;13(1):218.

127. Singh H, Ingersoll K, Gonder-Frederick L, Ritterband L. "Diabetes Just Tends to Take Over Everything": Experiences of Support and Barriers to Diabetes Management for Pregnancy in Women With Type 1 Diabetes. Diabetes Spectr. 2019 May;32(2):118–24.

128. Lawton J, Kirkham J, Rankin D, White DA, Elliott J, Jaap A, et al. Who gains clinical benefit from using insulin pump therapy? A qualitative study of the perceptions and views of health professionals involved in the Relative Effectiveness of Pumps over MDI and Structured Education (REPOSE) trial. Diabet Med. 2016 Feb;33(2):243–51.

129. Lawton J, Kimbell B, Rankin D, Ashcroft NL, Varghese L, Allen JM, et al. Health professionals' views about who would benefit from using a closed-loop system: a qualitative study. Diabetic Medicine. 2020;37(6):1030–7.

130. James S, Perry L, Gallagher R, Lowe J. Diabetes Educators: Perceived Experiences, Supports and Barriers to Use of Common Diabetes-Related Technologies. J Diabetes Sci Technol. 2016 Sept;10(5):1115–21.

131. Farrington C. Access to diabetes technology: the role of clinician attitudes. Lancet Diabetes Endocrinol. 2018 Jan;6(1):15.

132. Farrington C, Hovorka R, Murphy HR. Who Should Access Closed-Loop Technology? A Qualitative Study of Clinician Attitudes in England. Diabetes Technol Ther. 2020 May;22(5):404–10.

133. Farrington C, Murphy HR, Hovorka R. A qualitative study of clinician attitudes towards closed-loop systems in mainstream diabetes care in England. Diabet Med. 2020 June;37(6):1023–9.

134. McCorry NK, Hughes C, Spence D, Holmes VA, Harper R. Pregnancy planning and diabetes: a qualitative exploration of women's attitudes toward preconception care. J Midwifery Womens Health. 2012;57(4):396–402.

135. Dalfrà MG, Nicolucci A, Bisson T, Bonsembiante B, Lapolla A, QLISG (Quality of Life Italian Study Group). Quality of life in pregnancy and post-partum: a study in diabetic patients. Qual Life Res. 2012 Mar;21(2):291–8.

136. Farrington C, Stewart ZA, Barnard K, Hovorka R, Murphy HR. Experiences of closed-loop insulin delivery among pregnant women with Type 1 diabetes. Diabetic Medicine. 2017;34(10):1461–9.

137. Farrington C, Stewart Z, Hovorka R, Murphy H. Women's Experiences of Day-and-Night Closed-Loop Insulin Delivery During Type 1 Diabetes Pregnancy. J Diabetes Sci Technol. 2018 Oct 5;12(6):1125–31.

138. Bradley C, Lewis KS, Jennings AM, Ward JD. Scales to measure perceived control developed specifically for people with tablet-treated diabetes. Diabet Med. 1990;7(8):685–94.

139. Lee TTM, Collett C, Bergford S, Hartnell S, Scott EM, Lindsay RS, et al. Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes. New England Journal of Medicine. 2023 Oct 26;389(17):1566–78.

140. Lawton J, Blackburn M, Rankin D, Allen JM, Campbell FM, Leelarathna L, et al. Participants' Experiences of, and Views About, Daytime Use of a Day-and-Night Hybrid Closed-Loop System in Real Life Settings: Longitudinal Qualitative Study. Diabetes Technol Ther. 2019 Mar 1;21(3):119–27.

141. Rankin D, Kimbell B, Hovorka R, Lawton J. Adolescents' and their parents' experiences of using a closed-loop system to manage type 1 diabetes in everyday life: qualitative study. Chronic Illn. 2022 Dec;18(4):742–56.

142. Kimbell B, Rankin D, Hart RI, Allen JM, Boughton CK, Campbell F, et al. Parents' experiences of using a hybrid closed-loop system (CamAPS FX) to care for a very young child with type 1 diabetes: Qualitative study. Diabetes Res Clin Pract. 2022 May;187:109877.

143. Lawton J, Kimbell B, Closs M, Hartnell S, Lee TTM, Dover AR, et al. Listening to Women: Experiences of Using Closed-Loop in Type 1 Diabetes Pregnancy. Diabetes Technology & Therapeutics. 2023 Dec;25(12):845–55.

144. Lawton J, Rankin D, Hartnell S, Lee T, Dover AR, Reynolds RM, et al. Healthcare professionals' views about how pregnant women can benefit from using a closed-loop system: Qualitative study. Diabetic Medicine. 2023;40(5):e15072.

145. Rankin D, Hart RI, Kimbell B, Barnard-Kelly K, Brackenridge A, Byrne C, et al. Rollout of Closed-Loop Technology to Pregnant Women with Type 1 Diabetes:

Healthcare Professionals' Views About Potential Challenges and Solutions. Diabetes Technology & Therapeutics. 2023 Apr 1;25(4):260–9.

146. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006 Jan 1;3(2):77–101.

147. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000 Aug;23(4):334–40.

148. Sandelowski M. What's in a name? Qualitative description revisited. Res Nurs Health. 2010 Feb;33(1):77–84.

149. Breckenridge JP, Gianfrancesco C, De Zoysa N, Lawton J, Rankin D, Coates E. Mobilising knowledge between practitioners and researchers to iteratively refine a complex intervention (DAFNEplus) pre-trial: protocol for a structured, collaborative working group process. Pilot Feasibility Stud. 2018 Dec;4(1):120.

150. Rankin D, Kimbell B, Allen JM, Besser REJ, Boughton CK, Campbell F, et al. Adolescents' Experiences of Using a Smartphone Application Hosting a Closed-loop Algorithm to Manage Type 1 Diabetes in Everyday Life: Qualitative Study. J Diabetes Sci Technol. 2021 Sept;15(5):1042–51.

151. Gu J, Chaput KH, Dunlop A, Booth J, Feig DS, Donovan LE. Existing standardised questionnaires do not adequately capture quality-of-life outcomes of greatest importance for those living with type 1 diabetes in pregnancy. Diabet Med. 2023 Apr;40(4):e15044.

152. Rasmussen B, Dunning T, Hendrieckx C, Botti M, Speight J. Transition to motherhood in type 1 diabetes: design of the pregnancy and postnatal well-being in transition questionnaires. BMC Pregnancy Childbirth. 2013 Feb 27;13:54.

153. Rasmussen B, Nankervis A, Skouteris H, McNamara C, Nagle C, Steele C, et al. Psychosocial wellbeing among new mothers with diabetes: Exploratory analysis of the postnatal wellbeing in transition questionnaire. Sexual & Reproductive Healthcare. 2019 Dec;22:100457.

154. Lev-Ran A. Sharp temporary drop in insulin requirement after cesarean section in diabetic patients. Am J Obstet Gynecol. 1974 Dec 1;120(7):905–8.

155. Achong N, Duncan EL, McIntyre HD, Callaway L. Peripartum management of glycemia in women with type 1 diabetes. Diabetes Care. 2014 Feb;37(2):364–71.

156. Ringholm L, Mathiesen ER, Kelstrup L, Damm P. Managing type 1 diabetes mellitus in pregnancy--from planning to breastfeeding. Nat Rev Endocrinol. 2012 Nov;8(11):659–67.

157. Dashora U, Murphy HR, Temple RC, Stanley KP, Castro E, George S, et al. Managing hyperglycaemia during antenatal steroid administration, labour and birth in pregnant women with diabetes. Diabet Med. 2018 Aug;35(8):1005–10.

158. Nørgaard SK, Nørgaard K, Roskjær AB, Mathiesen ER, Ringholm L. Insulin Pump Settings During Breastfeeding in Women with Type 1 Diabetes. Diabetes Technol Ther. 2020 Apr 1;22(4):314–20.

159. World Health Organisation. Infant and young child feeding [Internet]. 2021 [cited 2025 May 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/infant-and-young-child-feeding

160. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. The Lancet. 2016 Jan;387(10017):475–90.

161. Rooney BL, Schauberger CW. Excess pregnancy weight gain and long-term obesity: one decade later. Obstet Gynecol. 2002 Aug;100(2):245–52.

162. Howie PW, Forsyth JS, Ogston SA, Clark A, Florey CD. Protective effect of breast feeding against infection. BMJ. 1990 Jan 6;300(6716):11–6.

163. Mayer-Davis EJ, Rifas-Shiman SL, Zhou L, Hu FB, Colditz GA, Gillman MW. Breast-feeding and risk for childhood obesity: does maternal diabetes or obesity status matter? Diabetes Care. 2006 Oct;29(10):2231–7.

164. Crume TL, Ogden L, Maligie M, Sheffield S, Bischoff KJ, McDuffie R, et al. Long-Term Impact of Neonatal Breastfeeding on Childhood Adiposity and Fat Distribution Among Children Exposed to Diabetes In Utero. Diabetes Care. 2011 Feb 17;34(3):641–5.

165. Rosenbauer J, Herzig P, Giani G. Early infant feeding and risk of type 1 diabetes mellitus-a nationwide population-based case-control study in pre-school children. Diabetes Metab Res Rev. 2008;24(3):211–22.

166. Neubauer SH. Lactation in insulin-dependent diabetes. Prog Food Nutr Sci. 1990;14(4):333–70.

167. Whichelow MJ, Doddridge MC. Lactation in diabetic women. Br Med J (Clin Res Ed). 1983 Sept 3;287(6393):649–50.

168. Davies HA, Clark JD, Dalton KJ, Edwards OM. Insulin requirements of diabetic women who breast feed. BMJ. 1989 May 20;298(6684):1357–8.

169. Saez-de-Ibarra L, Gaspar R, Obesso A, Herranz L. Glycaemic behaviour during lactation: postpartum practical guidelines for women with type 1 diabetes. Pract Diab Int. 2003 Oct;20(8):271–5.

170. Stage E, Nørgård H, Damm P, Mathiesen E. Long-term breast-feeding in women with type 1 diabetes. Diabetes Care. 2006 Apr;29(4):771–4.

171. Riviello C, Mello G, Jovanovic LG. Breastfeeding and the Basal Insulin Requirement in Type 1 Diabetic Women. Endocrine Practice. 2009 Apr 1;15(3):187–93.

172. Inkster B, Elder J, Alexander C, Osborne L, Zammitt NN, Frier BM. Post-partum hypoglycaemia in lactating women with type 1 diabetes: a pilot study using continuous glucose monitoring. British Journal of Diabetes. 2015 Sept 1;15(3):119–22.

173. Roeder HA, Moore TR, Ramos GA. Changes in Postpartum Insulin Requirements for Patients with Well-Controlled Type 1 Diabetes. Am J Perinatol. 2016 June;33(7):683–7.

174. Achong N, McIntyre HD, Callaway L, Duncan EL. Glycaemic behaviour during breastfeeding in women with Type 1 diabetes. Diabet Med. 2016 July;33(7):947–55.

175. Ringholm L, Roskjær AB, Engberg S, Andersen HU, Secher AL, Damm P, et al. Breastfeeding at night is rarely followed by hypoglycaemia in women with type 1 diabetes using carbohydrate counting and flexible insulin therapy. Diabetologia. 2019 Mar;62(3):387–98.

176. Skajaa GØ, Kampmann U, Ovesen PG, Fuglsang J. Breastfeeding and insulin requirements in women with Type 1 diabetes mellitus in the first year postpartum. Acta Diabetol. 2023 Mar 29;60(7):899–906.

177. Fresa R, Bitterman O, Cavallaro V, Di Filippi M, Dimarzo D, Mosca C, et al. An automated insulin delivery system from pregestational care to postpartum in women with type 1 diabetes. Preliminary experience with telemedicine in 6 patients. Acta Diabetol. 2024 Sept;61(9):1185–94.

178. Webster J, Moore K, McMullan A. Breastfeeding outcomes for women with insulin dependent diabetes. J Hum Lact. 1995 Sept;11(3):195–200.

179. Schoen S, Sichert-Hellert W, Hummel S, Ziegler AG, Kersting M. Breastfeeding duration in families with type 1 diabetes compared to non-affected families: results from BABYDIAB and DONALD studies in Germany. Breastfeed Med. 2008 Sept;3(3):171–5.

180. Finkelstein SA, Keely E, Feig DS, Tu X, Yasseen AS, Walker M. Breastfeeding in women with diabetes: lower rates despite greater rewards. A population-based study. Diabet Med. 2013 Sept;30(9):1094–101.

181. Misita D, Yamamoto JM, Yuan Y, Donovan LE, Bell RC, Jarman M. An exploration of differences in infant feeding practices among women with and without diabetes in pregnancy: A mixed-methods study. Diabetic Medicine. 2021;38(11):e14635.

182. McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew MJ. Infant Feeding Survey 2010: Summary. 2012;

183. Office for Health Improvement and Disparities. GOV.UK. 2023 [cited 2024 Sept 4]. Breastfeeding at 6 to 8 weeks after birth: annual data April 2022 to March 2023. Available from: https://www.gov.uk/government/statistics/breastfeeding-at-6-to-8-weeks-after-birth-annual-data-april-2022-to-march-2023

184. The NHS Information Centre, IFF Research. Infant Feeding Survey - 2010, Early results [Internet]. [cited 2024 Sept 4]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/infant-feeding-survey/infant-feeding-survey-2010-early-results

185. Sparud-Lundin C, Wennergren M, Elfvin A, Berg M. Breastfeeding in women with type 1 diabetes: exploration of predictive factors. Diabetes Care. 2011 Feb;34(2):296–301.

186. Sorkio S, Cuthbertson D, Bärlund S, Reunanen A, Nucci AM, Berseth CL, et al. Breastfeeding patterns of mothers with type 1 diabetes: results from an infant feeding trial. Diabetes/Metabolism Research and Reviews. 2010;26(3):206–11.

187. Cordero L, Oza-Frank R, Stenger MR, Landon MB, Nankervis CA. Decreasing NICU admissions of asymptomatic infants of women with pregestational diabetes mellitus improves breastfeeding initiation rates. J Neonatal Perinatal Med. 2018;11(2):155–63.

188. Rasmussen B, Nankervis A, Skouteris H, McNamara C, Nagle C, Steele C, et al. Factors associated with breastfeeding to 3 months postpartum among women with type 1 and type 2 diabetes mellitus: An exploratory study. Women Birth. 2020 May;33(3):e274–9.

189. Cordero L, Stenger MR, Blaney SD, Finneran MM, Nankervis CA. Prior breastfeeding experience and infant feeding at discharge among women with pregestational diabetes mellitus. J Neonatal Perinatal Med. 2020;13(4):563–70.

190. Berg M, Erlandsson LK, Sparud-Lundin C. Breastfeeding and its impact on daily life in women with type 1 diabetes during the first six months after childbirth: a prospective cohort study. Int Breastfeed J. 2012 Dec;7(1):20.

191. Rasmussen B, Skouteris H, Berg M, Nagle C, Morris H, Nankervis A, et al. Breastfeeding practices in women with type 1 diabetes: a discussion of the psychosocial factors and policies in Sweden and Australia. Women Birth. 2015 Mar;28(1):71–5.

192. Fallon A, Dunne F. Breastfeeding practices that support women with diabetes to breastfeed. Diabetes Res Clin Pract. 2015 Oct;110(1):10–7.

193. Sparud-Lundin C, Berg M. Extraordinary exposed in early motherhood - a qualitative study exploring experiences of mothers with type 1 diabetes. BMC Womens Health. 2011 Apr 7;11:10.

194. Edwards H, Speight J, Bridgman H, Skinner TC. The pregnancy journey for women with type 1 diabetes: a qualitative model from contemplation to motherhood. Practical Diabetes. 2016;33(6):194–199a.

195. Linden K, Berg M, Adolfsson A, Sparud-Lundin C. Well-being, diabetes management and breastfeeding in mothers with type 1 diabetes – An explorative analysis. Sexual & Reproductive Healthcare. 2018 Mar;15:77–82.

196. National Institute for Health and Care Excellence. Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. Technology appraisal guidance [Internet]. 2023 Dec 19; Available from: https://www.nice.org.uk/guidance/ta943/resources/hybrid-closed-loop-systems-for-managing-blood-glucose-levels-in-type-1-diabetes-pdf-82615666856389

197. Donovan LE, Feig DS, Lemieux P, Murphy HR, Bell RC, Sigal RJ, et al. A Randomized Trial of Closed-Loop Insulin Delivery Postpartum in Type 1 Diabetes. Diabetes Care. 2023 Dec;46(12):2258–66.

198. Polsky S, Buschur E, Dungan K, Garcetti R, Nease E, Malecha E, et al. Randomized Trial of Assisted Hybrid Closed-Loop Therapy Versus Sensor-Augmented Pump Therapy in Pregnancy. Diabetes Technol Ther. 2024 Aug;26(8):547–55.

199. Quintanilha M, Yamamoto JM, Aylward B, Feig DS, Lemieux P, Murphy HR, et al. Women's and Partners' Experiences with a Closed-Loop Insulin Delivery System to

Manage Type 1 Diabetes in the Postpartum Period. Can J Diabetes. 2024 Sept 3;S1499-2671(24)00176-X.

200. Murphy HR. 2020 NICE guideline update: Good news for pregnant women with type 1 diabetes and past or current gestational diabetes. Diabetic Medicine. 2021;38(6):e14576.

201. Scott EM, Murphy HR, Kennedy K, Kar P. CONCEPTT to care: the science of implementation in diabetes care. Lancet Diabetes Endocrinol. 2024 Apr;12(4):222–5.

202. Haidar A, Elleri D, Kumareswaran K, Leelarathna L, Allen JM, Caldwell K, et al. Pharmacokinetics of insulin aspart in pump-treated subjects with type 1 diabetes: reproducibility and effect of age, weight, and duration of diabetes. Diabetes Care. 2013 Oct;36(10):e173-174.

203. The Lancet. Non-communicable diseases in reproductive care. The Lancet. 2024 July;404(10448):95.

204. Sayres S, Visentin L. Breastfeeding: uncovering barriers and offering solutions. Current Opinion in Pediatrics. 2018 Aug;30(4):591.

205. Giannoulaki P, Kotzakioulafi E, Nakas A, Kontoninas Z, Evripidou P, Didangelos T. Use of Advanced Hybrid Closed-Loop System during Pregnancy: Strengths and Limitations of Achieving a Tight Glycemic Control. J Clin Med. 2024 Mar 1;13(5):1441.

206. Munda A, Kovacic C, Pongrac Barlovic D. Real-world data on the Minimed 780G advanced hybrid closed-loop system use during type 1 diabetes pregnancy: One centre observational study. Journal of Diabetes and its Complications. 2024 Aug;38(8):108795.

207. Benhalima K, Beunen K, Wilder NV, Ballaux D, Vanhaverbeke G, Taes Y, et al. Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial. Lancet Diabetes Endocrinol. 2024 June 1;12(6):390–403.

208. Quirós C, Herrera Arranz MT, Amigó J, Wägner AM, Beato-Vibora PI, Azriel-Mira S, et al. Real-World Evidence of Off-Label Use of Commercially Automated Insulin Delivery Systems Compared to Multiple Daily Insulin Injections in Pregnancies Complicated by Type 1 Diabetes. Diabetes Technology & Therapeutics. 2024 Aug;26(8):596–606.

209. Perea V, Quirós C, Herrera-Arranz MT, Azriel-Mira S, Wägner AM, Beato-Vibora P, et al. Pregnancy outcomes with the pregestational use of Minimed 780G compared to Minimed 640G: findings from a multicenter cohort study. Acta Diabetol [Internet]. 2024 Dec 4 [cited 2025 Jan 31]; Available from: https://link.springer.com/10.1007/s00592-024-02430-x

210. Beunen K, Van Wilder N, Ballaux D, Vanhaverbeke G, Taes Y, Aers XP, et al. Closed-loop insulin delivery in pregnant women with type 1 diabetes (CRISTAL): a multicentre randomized controlled trial - study protocol. BMC Pregnancy Childbirth. 2023 Mar 16;23(1):180.

211. ClinicalTrials.gov [Internet]. 2024 [cited 2025 Mar 25]. Closed-loop Insulin Delivery by Glucose Responsive Computer Algorithms In Type 1 Diabetes Pregnancies (CIRCUIT). Available from: https://clinicaltrials.gov/study/NCT04902378

212. Voerman E, Santos S, Inskip H, Amiano P, Barros H, Charles MA, et al. Association of Gestational Weight Gain With Adverse Maternal and Infant Outcomes. JAMA. 2019 May 7;321(17):1702–15.

213. Goldstein RF, Abell SK, Ranasinha S, Misso ML, Boyle JA, Harrison CL, et al. Gestational weight gain across continents and ethnicity: systematic review and meta-analysis of maternal and infant outcomes in more than one million women. BMC Medicine. 2018 Aug 31;16(1):153.

214. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet. 2006 Sept 30;368(9542):1164–70.

215. NHS England [Internet]. 2024 [cited 2025 Mar 26]. Hybrid closed loop technologies: 5-year implementation strategy. Available from: https://www.england.nhs.uk/long-read/hybrid-closed-loop-technologies-5-year-implementation-strategy/

216. NHS England. NHS England » Saving babies' lives: version 3 [Internet]. 2025 [cited 2025 Apr 29]. Available from: https://www.england.nhs.uk/long-read/saving-babies-lives-version-3-2/

217. Zakiyah N, Tuytten R, Baker PN, Kenny LC, Postma MJ, Asselt ADI van, et al. Early cost-effectiveness analysis of screening for preeclampsia in nulliparous women: A modelling approach in European high-income settings. PLOS ONE. 2022 Apr 21;17(4):e0267313.

218. Gallos I, Williams H, Price M, Pickering K, Merriel A, Tobias A, et al. Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis. Health Technol Assess. 2019 Feb;23(9):1–356.

219. NHS England. National Cost Collection for the NHS: 2023/24 National Cost Collection data. [cited 2025 Mar 30]. NHS England » National Cost Collection for the NHS. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

220. Campbell HE, Kurinczuk JJ, Heazell A, Leal J, Rivero-Arias O. Healthcare and wider societal implications of stillbirth: a population-based cost-of-illness study. BJOG. 2018 Jan;125(2):108–17.

221. Ahmed RJ, Gafni A, Hutton EK, Hu ZJ, Sanchez JJ, Murphy HR, et al. The cost implications of continuous glucose monitoring in pregnant women with type 1 diabetes in 3 Canadian provinces: a posthoc cost analysis of the CONCEPTT trial. CMAJ Open. 2021;9(2):E627–34.

222. Murphy HR, Feig DS, Sanchez JJ, de Portu S, Sale A. Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes. Diabet Med. 2019 Dec;36(12):1652–8.

223. National Institute for Health and Care Excellence. Intrapartum care for healthy women and babies. NICE guideline [Internet]. 2017; Available from: https://www.nice.org.uk/guidance/cg190/resources/intrapartum-care-for-healthy-women-and-babies-pdf-35109866447557

224. Dashora U, Rafique S, Tharayil G, Jones S, Castro E, Sathiskumar P. The feasibility and impact of implementing NICE guidance on diabetes control during delivery. Br J Diabetes. 2017 Aug 20;17(3):100.

225. Balsells M, Corcoy R, Adelantado JM, García-Patterson A, Altirriba O, de Leiva A. Gestational diabetes mellitus: metabolic control during labour. Diabetes Nutr Metab. 2000 Oct;13(5):257–62.

226. Lepercq J, Abbou H, Agostini C, Toubas F, Francoual C, Velho G, et al. A standardized protocol to achieve normoglycaemia during labour and delivery in women with type 1 diabetes. Diabetes & Metabolism. 2008 Feb 1;34(1):33–7.

227. Modi A, Levy N, Hall GM. Controversies in the peripartum management of diabetes. Anaesthesia. 2016;71(7):750–5.

228. Joint British Diabetes Societies for Inpatient Care. Managing diabetes and hyperglycaemia during labour and birth. 2023 Feb [cited 2025 Apr 27]; Available from: https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_Guidelines_Current/JBDS_12_Managing_diabetes_and_hyperglycaemia_during_labour_and_birth_with_diabetes_February_2023.pdf

229. Beunen K, Gillard P, Van Wilder N, Ballaux D, Vanhaverbeke G, Taes Y, et al. Advanced Hybrid Closed-Loop Therapy Compared With Standard Insulin Therapy Intrapartum and Early Postpartum in Women With Type 1 Diabetes: A Secondary Observational Analysis From the CRISTAL Randomized Controlled Trial. Diabetes Care. 2024 Sept 27;dc241320.

230. Haidar A, Tsoukas MA, Bernier-Twardy S, Yale JF, Rutkowski J, Bossy A, et al. A Novel Dual-Hormone Insulin-and-Pramlintide Artificial Pancreas for Type 1 Diabetes: A Randomized Controlled Crossover Trial. Diabetes Care. 2020 Mar;43(3):597–606.

231. Mosquera-Lopez C, Wilson LM, El Youssef J, Hilts W, Leitschuh J, Branigan D, et al. Enabling fully automated insulin delivery through meal detection and size estimation using Artificial Intelligence. npj Digit Med. 2023 Mar 13;6(1):1–7.

232. Boughton CK, Hartnell S, Lakshman R, Nwokolo M, Wilinska ME, Ware J, et al. Fully Closed-Loop Glucose Control Compared With Insulin Pump Therapy With Continuous Glucose Monitoring in Adults With Type 1 Diabetes and Suboptimal Glycemic Control: A Single-Center, Randomized, Crossover Study. Diabetes Care. 2023 Aug 24;46(11):1916–22.

233. Persson M, Pasupathy D, Hanson U, Norman M. Birth size distribution in 3,705 infants born to mothers with type 1 diabetes: a population-based study. Diabetes Care. 2011 May;34(5):1145–9.

234. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. Int J Gynaecol Obstet. 2004 Dec;87(3):220–6.

235. Weissmann-Brenner A, Simchen MJ, Zilberberg E, Kalter A, Weisz B, Achiron R, et al. Maternal and neonatal outcomes of large for gestational age pregnancies. Acta Obstetricia et Gynecologica Scandinavica. 2012;91(7):844–9.

236. Yamamoto JM, Kallas-Koeman MM, Butalia S, Lodha AK, Donovan LE. Large-for-gestational-age (LGA) neonate predicts a 2.5-fold increased odds of neonatal hypoglycaemia in women with type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2017;33(1):e2824.

237. Grossman L, Pariente G, Baumfeld Y, Yohay D, Rotem R, Weintraub AY. Trends of changes in the specific contribution of selected risk factors for shoulder dystocia over a period of more than two decades. Journal of Perinatal Medicine. 2020 July 1;48(6):567–73.

238. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol. 2007 Apr 15;165(8):849–57.

239. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005 Mar;115(3):e290-296.

240. Law GR, Ellison GTH, Secher AL, Damm P, Mathiesen ER, Temple R, et al. Analysis of continuous glucose monitoring in pregnant women with diabetes: distinct temporal patterns of glucose associated with large-for-gestational-age infants. Diabetes Care. 2015 July 1;38(7):1319–25.

241. Misra S, Ke C, Srinivasan S, Goyal A, Nyriyenda MJ, Florez JC, et al. Current insights and emerging trends in early-onset type 2 diabetes. The Lancet Diabetes & Endocrinology. 2023 Oct 1;11(10):768–82.

242. Koye DN, Ling J, Dibato J, Khunti K, Montvida O, Paul SK. Temporal Trend in Young-Onset Type 2 Diabetes-Macrovascular and Mortality Risk: Study of U.K. Primary Care Electronic Medical Records. Diabetes Care. 2020 Sept;43(9):2208–16.

243. Zhao M, Song L, Sun L, Wang M, Wang C, Yao S, et al. Associations of Type 2 Diabetes Onset Age With Cardiovascular Disease and Mortality: The Kailuan Study. Diabetes Care. 2021 June 1;44(6):1426–32.

244. Sattar N, Rawshani A, Franzén S, Rawshani A, Svensson AM, Rosengren A, et al. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. Circulation. 2019 May 7;139(19):2228–37.

245. Gallimore ID, Matthews RJ, Page GL, Smith LK, Fenton AC, Knight M, Smith PW, Redpath S, Manktelow BN, on behalf of the MBRRACE-UK Collaboration. MBRRACE-UK Perinatal Mortality Surveillance: UK Perinatal Deaths of Babies Born in 2023 - State of the Nation Report. Leicester: TIMMS, Department of Population Health Sciences, University of Leicester.; 2025.

Appendix

Appendix 1 AiDAPT trial protocol including postnatal extension

NORWICH CTU

Automated **i**nsulin **D**elivery **A**mongst
Pregnant women with **T**ype 1 diabetes

Evaluation of the biomedical and psychosocial impact of automated Closed-Loop (Artificial Pancreas) insulin delivery in women with type 1 diabetes during pregnancy

Version	5.0
Date	22nd October 2021
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Trial registration	ISRCTN 56898625
IRAS project ID	240380

Authorisation: Chief Investigator

Name	Professor Helen R Murphy
Role	Chief Investigator
Signature	
Date	23/11/2021

This protocol has been written in accordance with current ISO 14155:2011 standard

Authorisation: Sponsor

Name	Julie Dawson
Role	Sponsor Representative
Signature	DocuSigned by: Julie Dawson 4CBAB366CF354A2...
Date	27 January 2022

Authorisation: CTU Director or Representative

Name	Professor Ann Marie Swart
Role	Norwich CTU Director
Signature	AMcS.
Date	23/11/2021

Authorisation: Trial Statistician

Name	Professor Lee Shepstone
Role	Norwich CTU Trial Statistician
Signature	
Date	

Authorisation: Jaeb Trial Statistician

Name	Dr Craig Kollman
Role	Jaeb Trial Statistician
Signature	
Date	

Table of Contents

2 Administrative information

This Clinical Investigation Plan was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol Template Version 4. It describes the AiDAPT trial, sponsored by the Norfolk and Norwich University Hospitals NHS Foundation Trust and coordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The Clinical Investigation Plan should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this Clinical Investigation Plan, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials[1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

2.1 Compliance

The trial will be conducted in compliance with the approved Clinical Investigation Plan, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Medical Devices Regulations 2002, International Standard ISO 14155 (as far as relevant), the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the Data Protection Act 2018, the General Data Protection Regulation (GDPR) (EU) 2016/679, and the National Health Service (NHS) UK Policy Framework for Health and Social Care Research and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of any deviation to the study, so that NCTU can fulfil its requirement to report the deviation if necessary.

NCTU will report to the ethics committee any deviation that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

2.2 Sponsor

Norfolk and Norwich University Hospital NHS Foundation Trust is the trial sponsor and has delegated responsibility for the overall management of the AiDAPT trial to the Chief Investigator and NCTU. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator or via the trial team.

2.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN Number: 56898625
Date of Registration in Primary Registry	10/04/2018
Secondary Identifying Numbers	IRAS No. 240380
Source of Monetary or Material Support	NIHR Efficacy and Mechanism Evaluation Programme 16/35/01
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Contact for Public Queries	aidapt.trial@uea.ac.uk
Contact for Scientific Queries	Professor Helen R Murphy MBBChBAO, FRACP, MD Honorary Consultant Physician Norfolk and Norwich University Hospital NHS Foundation Trust Cambridge University Hospital NHS Foundation Trust Professor of Medicine (Diabetes and Antenatal Care) Norwich Medical School Floor 2, Bob Champion Research and Education Building James Watson Road University of East Anglia Norwich Research Park Norwich NR4 7UQ Tel: +44 (0)1603 591657 Mobile: +44 (0)7595 166 852 Email: Helen.Murphy@uea.ac.uk
Short Title or Acronym	AiDAPT – **A**utomated **i**nsulin **D**elivery **A**mongst **P**regnant women with **T**ype 1 diabetes
Scientific Title	Evaluation of the biomedical and psychosocial impact of automated Closed-Loop (Artificial Pancreas) insulin delivery in women with type 1 diabetes during pregnancy
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Pre-gestational type 1 diabetes during pregnancy

Intervention(s)	**Intervention Arm**: An automated closed-loop insulin delivery (AiD) system. **Control Arm**: A standard insulin delivery system which is either insulin pump (Continuous Subcutaneous Insulin Infusion - CSII) or multiple daily injections (MDI) without closed-loop.
Key Inclusion and Exclusion Criteria	Key inclusion criteria: 1. Between 18 and 45 years of age (inclusive). 2. A diagnosis of type 1 diabetes (T1D), as defined by WHO for at least 12 months. 3. A viable pregnancy confirmed by ultrasound, up to 13 weeks and 6 days gestation. 4. Currently on intensive insulin therapy (≥3 injections or CSII). 5. Willingness to use the study devices throughout the trial. 6. HbA1c level ≥48 mmol/mol (≥6.5%) at booking (first antenatal contact) and ≤86 mmol/mol (≤10%) at point of randomization. A continuous glucose monitor (CGM) or Libre glucose management indicator (GMI) ≥48 mmol/mol (≥6.5%) or ≤86 mmol/mol (≤10%) may also be used. 7. Able to provide informed consent. 8. Have access to email. Key exclusion criteria: 1. Non-type 1 diabetes. 2. Any other physical or psychological disease which, in the opinion of the investigator, is likely to interfere with the normal conduct and interpretation of the study results e.g. untreated coeliac disease or untreated hypothyroidism. 3. Current treatment with drugs known to interfere with glucose metabolism as judged by the investigator such as high dose systemic corticosteroids, non-selective beta-blockers and MAO inhibitors. 4. Known or suspected allergy against insulin. 5. Women with advanced nephropathy (eGFR <45), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as judged by the investigator, that is likely to interfere with the normal conduct of the study and interpretation of study results. 6. Very good or very poor glycaemic control i.e. first antenatal HbA1c <48 mmol/mol (<6.5%) and current HbA1c >10% (>86 mmol/mol). A CGM or Libre GMI <48 mmol/mol (<6.5%) or >86 mmol/mol (>10%) may also be used. Women who enter pregnancy with HbA1c or GMI >10% (>86 mmol/mol) may participate if they achieve HbA1c or GMI ≤10% (≤86 mmol/mol) before randomization.

	7. Total daily insulin dose ≥1.5 IU/kg. 8. Severe visual or hearing impairment. 9. Unable to speak and understand English.
Study Type	An open-label, multi-centre, randomized, two-arm parallel group trial comparing automated closed-loop and standard insulin delivery for pregnant women with type 1 diabetes.
Target Sample Size	124 (62 per arm)
Primary Outcome(s)	The time spent with glucose levels between 3.5-7.8 mmol/L based on CGM measures (Time In Range TIR 3.5-7.8mmol/L) from 16 weeks gestation until delivery.
Key Secondary Outcomes	1. CGM glucose measures (time in, above and below target range, Hypoglycaemia events, Low Blood Glucose Index (LBGI), glucose variability measures (CV, SD), HbA1c. 2. Diabetic ketoacidosis. 3. Severe hypoglycaemia episodes. 4. The number and severity of episodes of adverse device effect. 5. Hospital length of stay (maternal). 6. Mode of delivery, gestational age at delivery, infant birth weight, incidence of large for gestational age (LGA), and small for gestational age (SGA). 7. Neonatal morbidity (hypoglycaemia, jaundice, respiratory distress). 8. Neonatal intensive care unit (NICU) admission. 9. Hospital length of stay (infant). 10. Adverse events including pregnancy loss <24 weeks, stillbirth, neonatal death.
Key Outcomes (Postpartum Period)	The key post-partum analysis will evaluate the time spent in the target glucose range (CGM TIR 3.9 – 10.0 mmol/l) between delivery and 6 months postpartum. Other exploratory outcomes include: • CGM glucose measures (time in, above and below target range, Hypoglycaemia events, Low Blood Glucose Index (LBGI), glucose variability measures (CV, SD), mean CGM glucose. • Insulin dose (basal, bolus, and total) changes

2.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

2.4.1 Clinical Investigation Plan Contributors

Name	Affiliation	Role
Professor Helen Murphy	UEA, Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH), Cambridge University Hospitals NHS Foundation Trust (CUHFT)	Chief Investigator
Professor Roman Hovorka	University of Cambridge	Device Technology Lead
Professor Julia Lawton	University of Edinburgh	Psychosocial lead
Dr Craig Kollman	Jaeb Center for Health Research	Jaeb Trial Statistician
Professor Lee Shepstone	UEA – Norwich Clinical Trials Unit	NCTU Trial Statistician

2.4.2 Trial Sponsor and Funders

Name	Affiliation	Role
Julie Dawson	Norfolk and Norwich University Hospitals NHS Foundation Trust	Sponsor Representative
Michael Sheridan	Norfolk and Norwich University Hospitals NHS Foundation Trust	Research Study and Recruitment Facilitator
Roderick Delanougerede	NIHR	Funder Representative

2.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Professor Helen Murphy	UEA, NNUH, CUHFT	Chief Investigator
Matt Hammond	UEA – Norwich Clinical Trials Unit	Senior Trial Manager
Corinne Collett	UEA – Norwich Clinical Trials Unit	Trial Manager
Emma Flanagan	UEA – Norwich Clinical Trials Unit	Junior Trial Manager

2.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Helen Murphy	UEA, NNUH, CUHFT	Chief Investigator

Professor Roman Hovorka	University of Cambridge	Device Technology Lead
Professor Eleanor Scott	University of Leeds	Type 1 diabetes in pregnancy expertise
Professor David McCance	Royal Victoria Hospital, Belfast	Type 1 diabetes in pregnancy expertise
Dr Robert Lindsay	University of Glasgow	Type 1 diabetes in pregnancy expertise
Professor Katharine Barnard	Bournemouth University	Health Psychologist
Professor Ann Marie Swart	UEA – Norwich Clinical Trials Unit	Clinical Trials Unit Director
Professor Julia Lawton	Usher Institute of Population Health Sciences	Medical sociology and qualitative methodology
Professor Fiona Denison	MRC Centre for Reproductive Health	Obstetrics expertise
Dr Katharine Hunt	King's College Hospital NHS Foundation Trust	Clinical and academic diabetes expertise
Dr Craig Kollman	Jaeb Center for Health Research	Jaeb Trial Statistician
Professor Lee Shepstone	UEA – Norwich Clinical Trials Unit	NCTU Trial Statistician
Matt Hammond	UEA – Norwich Clinical Trials Unit	Senior Trial Manager
Corinne Collett	UEA – Norwich Clinical Trials Unit	Trial Manager
Martin Pond	UEA – Norwich Clinical Trials Unit	Head of Data Management
Sara Hartnell	Cambridge University Hospitals NHS Foundation Trust	Lead diabetes educator

2.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Professor Ponnusamy Saravanan	University of Warwick	Independent Chair
Dr Rosemary Temple	Norfolk & Norwich (now retired)	Independent Member
Professor Marian Knight	National Perinatal Epidemiology Unit, University of Oxford	Independent Member
Dr Goher Ayman	National Perinatal Epidemiology Unit, University of Oxford	PPI Representative
Mrs Sarah Cains		PPI Representative
Professor Helen Murphy	UEA	Member

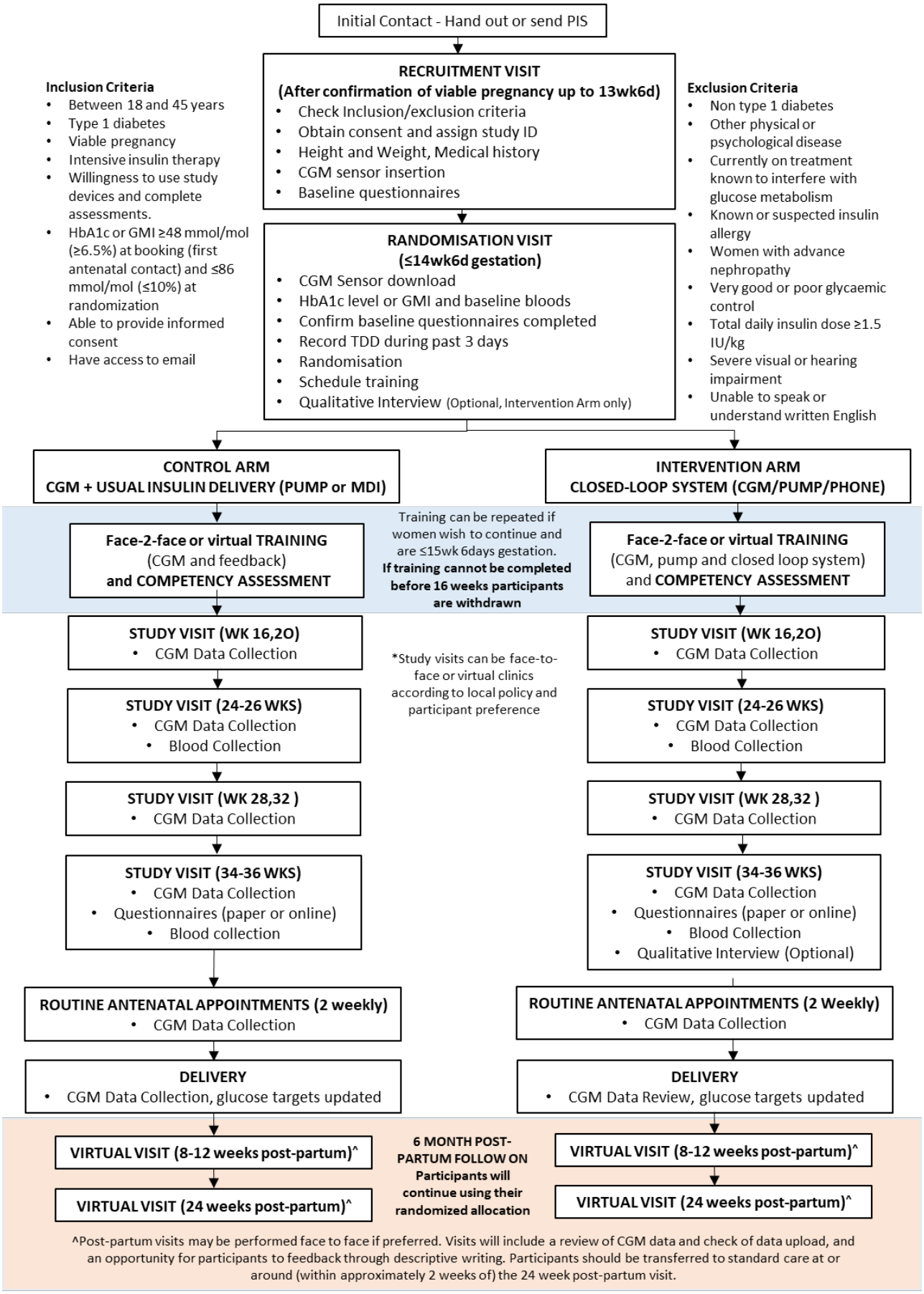
2.4.6 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Professor Jim Thornton	University of Nottingham	Independent Chair (academic obstetrician)
Dr Debbie Cooke	University of Surrey	Independent Member (psychosocial)
Professor Graham Law	University of Lincoln	Independent Member (statistician)
Dr Jackie Elliott	University of Sheffield	Independent Member (clinician in diabetes)

2.4.7 Psychosocial Oversight Groups

Name	Affiliation	Role and responsibilities
Professor Julia Lawton	Usher Institute of Population Health Sciences	Psychosocial Lead
Professor Katharine Barnard	Bournemouth University	Health Psychologist
Professor Fiona Denison	MRC Centre for Reproductive Health	Obstetrics expertise
Professor Helen Murphy	UEA	Chief Investigator
Katy Davenport	Cambridge University Hospitals NHS Foundation Trust	Diabetes Specialist Nurse
Caroline Byrne	Cambridge University Hospitals NHS Foundation Trust	Diabetes Specialist Nurse

3 Trial Diagram



4 Abbreviations

ADE	Adverse Device Event
AE	Adverse Event
AiD	Automated insulin delivery
AUC	Area under the curve
CE	Conformité Européenne (CE-mark)
CI	Chief Investigator
CIP	Clinical Investigation Plan
CGM	Continuous glucose monitoring
CL	Closed-loop
CRF	Case Report Form
CSII	Continuous subcutaneous insulin infusion
DDS	Diabetes distress scale
DMC	Data Management Committee
EQ5D	Euro Health-Related Quality of Life Descriptive system
EU	European Union
GCP	Good Clinical Practice
GMI	Glucose Management Indicator
HFS II	Hypoglycaemia Fear Survey II
HBGI	High Blood Glucose Index
HRA	Health Research Authority
IMD	Investigational Medicinal Device
INSPIRE	Insulin delivery Systems: Perspectives, Ideas, Reflections and Expectations
ISO	International Organisation for Standardisation
ITT	Intention to Treat
JCHR	Jaeb Center for Health Research
LBGI	Low Blood Glucose Index
MDI	Multiple daily injections
MHRA	Medicines and Healthcare products Regulatory Agency
MPC	Model predictive control algorithm
NCTU	Norwich Clinical Trials Unit
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
PROMS	Patient Reported Outcome Measures
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T1D	Type 1 diabetes
TMF	Trial Master File
TAR	Time Above Range
TBR	Time Below Range
TIR	Time In Range

TMG	Trial Management Group
TT	Trial Team
ToR	Terms of Reference
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
UEA	University of East Anglia
VRIII	Variable Rate Intravenous Insulin Infusion

5 Introduction

5.1 Background and Rationale

To deliver healthy infants, women with diabetes are advised to aim for near normal blood glucose levels (3.5-7.8 mmol/L). The importance of avoiding hyperglycaemia to reduce preterm delivery, neonatal morbidity and large for gestational age (infant birth weight >90th percentile) is well recognised (1). The incidence of large for gestational age in the offspring of women with type 1 diabetes remains 3.5-5 times greater than the general population (2), despite increased efforts to optimise glycaemic control using faster acting insulin analogues, insulin pumps and continuous glucose monitoring (CGM) (3-5).

Studies in pregnant women with and without diabetes suggest that for normal fetal growth mean blood glucose of 5.3 mmol/L is required throughout the second and third trimesters (6). Using CGM we have shown that pregnant women with type 1 diabetes spend an average 12 hrs/day or 50% time within the NICE previously recommended glucose target levels of 3.9-7.8 mmol/L, with mean CGM glucose levels of 7.1 mmol/L and 6.6 mmol/L during the second and third trimesters respectively (7). There is an urgent unmet need for better tools to improve glucose control and maternal infant health outcomes in type 1 diabetes pregnancy.

The three components of the closed-loop system are an insulin pump, a continuous glucose monitor (CGM) and a computer-based model predictive control (MPC) algorithm to compute information from the CGM into a recommended insulin dose. Closed-loop systems are designed to deliver insulin in response to CGM glucose levels and may help to bridge the gap between our expectations of tight glucose control and what is currently achievable using standard insulin pumps and injections.

In pregnancy, we have completed four pilot studies of automated closed-loop (artificial pancreas) insulin delivery (8-11). Together these studies provide data on 54 pregnant women with type 1 diabetes, 22 under carefully supervised clinical research facility conditions (CLIP_01, CLIP_02) and 32 in NHS hospital and real-life home settings (CLIP_03, CLIP_04). The phase I proof of concept study(CLIP_01) found that closed-loop could adjust overnight insulin delivery in pregnancy in early and late pregnancy (8) and over 24-hours (CLIP_02) incorporating carbohydrate-rich meals, snacks and physical activity (9).

We recently completed the first home feasibility study in pregnancy (CLIP_03), evaluating overnight closed-loop over 28 days compared with sensor augmented pump therapy in 16 pregnant women (10). Women using overnight closed-loop had significant improvement in nocturnal glucose control (23.00-07.00h), increasing time spent in the 3.5-7.8 mmol/l target range (TIR 3.5-7.8mmol/L) from 60 to 75% (p=0.002), with lower mean glucose (6.6 vs 7.4 mmol/l; p<0.009). They spent one third less time with glucose levels >7.8 mmol/l (24 vs 38%; p=0.005) and one half less time with glucose levels >10 mmol/l (7.4 vs 15.7%; p=0.004). There was no difference in the amount of time spent hypoglycaemic or in total daily doses of insulin (10).

In CLIP_04, we used the same randomized crossover study design to evaluate day-and-night closed-loop over 28 days compared with sensor augmented pump therapy in 16 pregnant women (11). Here we included a broader patient population including women with booking HbA1c levels above and below 7.5% (58 mmol/mol). We found that the proportion of time with glucose levels within target was comparable during closed-loop and control but that closed-loop was associated with

significantly less hypoglycaemia. All participants chose to continue using closed-loop, for at least some of the time, after the randomized crossover trial and 12/16 used closed-loop for up to 6 weeks post-partum (12).

Importantly, and unlike most early phase closed-loop (Artificial Pancreas) studies, we recruited women without prior technology experience (90% had no CGM experience and 50% had no insulin pump experience) and included women from ethnic minority and socially disadvantaged backgrounds (13). However, our phase II home trials used a randomized crossover design over a short duration (28 days) in a small number (n=32) of participants. Whilst our data suggest superior efficacy against CGM and insulin pump therapy in 3 antenatal diabetes clinics (Cambridge, Norwich, Ipswich), the CGM and insulin pump control group were not representative of the broader NHS population who currently use insulin injections (70%) and standard insulin pumps (30%), mostly without CGM (90%). Automated insulin delivery could be more effective in routine care settings and current recommendations suggest that pivotal trials should include normal care control groups (14).

The study design for CLIP_03 and CLIP_04 allowed women to continue using automated closed-loop, or any combination of the insulin pump and CGM devices, from after they finished the 28-day randomized crossover arms until the end of their pregnancy (and for up to 6 weeks post-partum in CLIP_04). To date, 30/32 (94%) women have chosen to continue closed-loop with one discontinuation for efficacy (one participant could achieve tighter glucose control using the pump and CGM) and one for device burdens (did not like wearing/carrying the devices). These non-randomized data provide insights into the feasibility of closed-loop over a longer time frame (approximately 6 months among 30 pregnant women).

To date, 32 women have delivered, and 27/32 (84%) used closed-loop to control their glucose levels in NHS hospital settings during and after delivery (10-12). Women who used closed-loop during labour and delivery spent 82.0% (IQR 49.3, 93.0) of time in the target range (TIR 3.5-7.8mmol/L), with a mean (SD) glucose level of 6.9 (1.4) mmol/L. This non-randomized feasibility data suggests that the automated closed-loop system can cope not only under steady-state glucose conditions but also under more challenging circumstances of changing insulin resistance during advanced pregnancy encompassing antenatal steroids, labour, delivery and the immediate post-partum period.

This trial focuses on determining the definitive proof of CLINICAL EFFICACY in women using automated closed-loop for approximately 28 weeks duration (10-38 weeks) throughout pregnancy in real-life NHS ANTENATAL CARE settings. It will also aim to understand more about women's and health care professionals' experiences of using automated insulin delivery in type 1 diabetes pregnancy and to provide estimates of its cost-effectiveness and cost-utility.

5.1.1 Research questions

1) What is the biomedical impact of an automated insulin delivery in pregnant women with type 1 diabetes?

    a. Does automated insulin delivery improve maternal glycaemic control during the second and third trimester, compared to a standard (insulin pump or injections) regimen of insulin delivery?

b. Is automated insulin delivery safe in terms of rates of adverse events, maternal hypoglycaemia and diabetic ketoacidosis?
c. Is the in-hospital use of automated insulin delivery by participants and NHS staff on obstetric wards and delivery unit as safe and effective as standard insulin pump, injections or intravenous insulin infusion?

2) What is the psychosocial impact of an automated closed-loop insulin delivery in pregnant women with type 1 diabetes?

a. What are women's experiences of using closed-loop to manage their diabetes?
b. How might closed-loop be improved for future use by pregnant women?
c. What information and support do staff need to help pregnant women with diabetes use closed-loop to best effect?

3) What are the potential costs and benefits of automated closed-loop insulin delivery?

a. Is automated insulin delivery cost-effective during type 1 diabetes pregnancy?
b. Does automated insulin delivery have an impact on quality adjusted life years (QALYs)?

5.1.2 Explanation for choice of comparators

5.1.2.1 Intervention

The intervention being evaluated in this trial is automated closed-loop insulin delivery (AiD). The closed-loop system comprises of three components: an insulin pump, a continuous glucose monitor (CGM) and a computer-based model predictive control (MPC) algorithm to compute information from the CGM into a recommended insulin dose. Closed-loop systems are designed to deliver insulin in response to CGM glucose levels and may help to improve glucose control above and beyond what is currently achievable using insulin pumps, injections and CGM without AiD.

The combination of devices to be used for automated insulin delivery are the best combination of devices currently available for this patient population.

5.1.2.2 Control

The control for this study will be self-directed insulin delivery for pregnant women with T1D, which is insulin pump or MDI. It is expected that both real-time CGM and Freestyle Libre will be increasingly used in routine care. To minimise between group differences according to intermittent and real-time CGM use, the control group will be provided with the same CGM as per the intervention group allowing for the same CGM glucose data to be obtained, recorded continuously and reviewed at 2-4 weekly study visits.

5.2 Objectives

5.2.1 Efficacy

To assess the clinical efficacy of automated insulin delivery in the home setting as compared with standard self-directed insulin delivery in pregnant women with T1D. The primary efficacy objective is to maintain glucose levels within the target range (TIR 3.5-7.8 mmol/L) based on the international consensus targets for subcutaneous CGM measures (15).

5.2.2 Safety objectives

To determine the impact of automated insulin delivery in terms of the frequency, duration and severity of:

1) Severe hypoglycaemia (defined as an event requiring assistance of another person actively to administer carbohydrate, glucagon or other resuscitative actions)
2) Diabetic ketoacidosis
3) Adverse device effect (see section 7 for definition).

5.2.3 Psychosocial objectives

To determine women's perception of automated insulin delivery in terms of diabetes self-management, fear of hypoglycaemia, sleep quality, pregnancy experiences and women's work and family lives. We will also explore health care professionals' experiences of using closed-loop in NHS hospital settings and provide recommendations to aid interpretation of trial data for refinements to, and rollout of closed-loop for use by future cohorts of pregnant women.

5.2.4 Health economic objectives

a) A cost-effectiveness study to estimate the additional cost per additional week of good glucose control based on CGM time in target range (TIR 3.5-7.8 mmol/l)
b) A cost-utility study using EQ-5D to estimate quality adjusted life years (QALYs)

The main components of resource use associated with the antenatal management of type 1 diabetes are likely to be the cost of measuring glucose and providing insulin and the costs of hospital based maternity and neonatal services. The cost of the closed-loop system will include the cost of the pump, CGM, and control algorithm. The additional cost of closed-loop device training will also be considered.

In addition to the costs of directly providing the intervention there may also be implications for maternity related health care use and hence costs. These costs would include antenatal clinic attendances, inpatient and outpatient visits associated with complications of pregnancy, length of stay for delivery and costs associated with any complication of delivery, and with neonatal complications.

5.3 Trial Design

An open-label, multi-centre, randomized, two-arm parallel group trial comparing automated closed-loop and standard insulin delivery.

124 pregnant women between 18 and 45 years of age with T1D of at least 12 months' duration on standard insulin delivery (CSII or MDI) will be recruited through outpatient antenatal diabetes clinics. Women fulfilling the eligibility criteria will be randomized to automated insulin delivery (AiD) or to continue standard patient-directed insulin delivery (CSII or MDI) without AiD. The study will take place within the home and NHS antenatal clinical settings. The main objective of this study is to evaluate the clinical efficacy of automated insulin delivery in the home setting, as compared to the use of standard insulin delivery.

The primary efficacy endpoint is the percentage time spent with glucose levels within the International consensus target range (TIR 3.5-7.8 mmol/L), as recorded by CGM across both arms.

Reduction in the time with glucose levels outside the target range and improvement in blood glucose control as assessed by HbA1c at 24-26 and 34-36 weeks gestation (where available) will be evaluated as secondary efficacy endpoints. Safety evaluation is focused on frequency, severity and duration of episodes of severe hypoglycaemia, diabetic ketoacidosis and adverse device effects. Obstetric and neonatal health outcomes will be documented at hospital discharge.

In addition, a mixed-methods study with quantitative patient reported outcome measures (PROMS) and in-depth qualitative interviews with trial staff and participants will be conducted to:

a. Explore women's experience of using automated insulin delivery to manage their diabetes during pregnancy
b. Explore health care professionals' experiences of using automated insulin delivery
c. Aid interpretation of trial data and provide recommendations for refinements to, and rollout of automated insulin delivery for use by future cohorts of pregnant women.

We also intend to undertake a preliminary health economic evaluation to estimate the cost-effectiveness and cost-utility of automated insulin delivery in type 1 diabetes pregnancy.

Women will be offered the opportunity to continue with their randomised allocations for 6 months after delivery of their baby(ies). See Appendix 1 for full details.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CI and NCTU.

6.1.1 Study Setting

Recruitment for this study will take place in NHS antenatal diabetes clinics. Participants will use the study devices in a home setting with support from the usual clinical care team. Participants may also continue to use the study devices during antenatal hospital admissions, including the delivery admission, and for 6 months post-partum.

Interviews will be conducted either by telephone or face to face at a mutually convenient location.

6.1.2 Site/Investigator Eligibility Criteria

Sites have been pre-selected to participate in this study based on their ability to recruit sufficient participants into similar studies in type 1 diabetes pregnancy. The trial team will provide sites with a copy of this Clinical Investigation Plan and relevant Investigator Brochures.

Trial sites will be issued with a pack of documentation needed by the Research and Development Department (R&D) of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the study.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an investigator statement to comply with the Clinical Investigation Plan for this trial (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any devices, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return.

6.2 Site approval and activation

Originally, the Medicines and Healthcare products Regulatory Agency (MHRA) required that details of all amendments including notification of new sites should be supplied to them and amendments could not be implemented until a notice of no objection was received. However, both Dexcom G6 and CamAPS FX app investigational devices have now been CE marked covering the purpose of the study investigation, therefore MHRA no longer require notification of amendments.

On receipt of the signed investigator statement, approved delegation of responsibilities log and staff contact details, and appropriate local approvals, written confirmation will be sent to the site PI. The Trial Manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the Clinical Investigation Plan as agreed by the Sponsor, HRA and, previously by the regulatory authority, and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved Clinical Investigation Plan, and communicate this to the trial team at NCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

124 pregnant women with T1D aged 18 to 45 years on intensive insulin therapy, either insulin pump or MDI, will be recruited from outpatient diabetes antenatal clinics or by direct contact with the clinical care team.

Potential participants will be identified by their treating clinicians, provided with study information leaflets either in person or by post/email and invited to join the study usually at least one week before the recruitment visit. They may also contact the clinical research team directly. All women will be offered the opportunity to discuss the advantages and disadvantages of study participation with a member of the research team and/or their diabetes physician/diabetes educator/obstetric physician/obstetrician. Consent to participate in the study will only be obtained when a viable pregnancy has been confirmed by ultrasound.

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to attempting to randomize the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

1. Between 18 and 45 years of age (inclusive).
2. A diagnosis of type 1 diabetes (T1D), as defined by WHO (a chronic condition in which the pancreas produces little or no insulin by itself, characterized by deficient insulin production and a requirement for daily administration of insulin), for at least 12 months.
3. A viable pregnancy confirmed by ultrasound, up to 13 weeks and 6 days gestation.

4. Currently on intensive insulin therapy (≥3 injections or CSII). This includes women using sensor augmented pumps and/or hybrid closed-loop systems other than CamAPS FX.
5. Willingness to use the study devices throughout the trial
6. HbA1c level ≥48 mmol/mol (≥6.5%) at booking (first antenatal contact) and ≤86 mmol/mol (≤10%) at point of randomization. A CGM or Libre GMI (glucose management indicator) ≥48 mmol/mol (≥6.5%) or ≤86 mmol/mol (≤10%) may also be used.
7. Able to provide informed consent.
8. Have access to email.

6.3.1.3 Participant Exclusion Criteria

1. Non-type 1 diabetes.
2. Any other physical or psychological disease which, in the opinion of the investigator, is likely to interfere with the normal conduct and interpretation of the study results e.g. untreated coeliac disease or untreated hypothyroidism.
3. Current treatment with drugs known to interfere with glucose metabolism as judged by the investigator such as high dose systemic corticosteroids, non-selective beta-blockers and MAO inhibitors.
4. Known or suspected allergy against insulin.
5. Women with advanced nephropathy (eGFR <45), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as judged by the investigator, that is likely to interfere with the normal conduct of the study and interpretation of study results.
6. Very good or very poor glycaemic control i.e. first antenatal HbA1c <48mmol/mol (<6.5%) and current HbA1c >86mmol/mol (>10%). A CGM or Libre GMI (glucose management indicator) <48 mmol/mol (<6.5%) or >86 mmol/mol (>10%) may also be used. Women who enter pregnancy with HbA1c or GMI >86 mmol/mol (>10%) may participate if they achieve HbA1c or GMI ≤86mmol/mol (≤10%) before randomization.
7. Total daily insulin dose ≥ 1.5 IU/kg at recruitment.
8. Severe visual or hearing impairment.
9. Unable to speak and understand English.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

The intervention will be conducted by site staff who are experienced in working with pregnant women with T1D. Full training in the study procedures and use of the closed-loop system will be provided to the local study team. Training modules for study staff are available at https://camdiab.cdep.org.uk/view/20/Webinars.htm. Booster training sessions will also be offered to site staff after the first few participants have been recruited at a site. An online booster training session is available - https://youtu.be/pKQArzzv5QA

6.3.1.5 Co-enrolment Guidance

Co-enrolment into interventional diabetes studies is not permitted, however co-enrolment is permitted for observational studies subject to the approval of the Trial Management Group.

6.3.1.6 Screening Procedures

Written informed consent to enter and be randomized into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and

BEFORE any trial-specific procedures. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

6.3.1.7 Screening logs

Participating sites will be expected to maintain records of all patients screened for the trial, including those who are not entered (for whom ID numbers are not obtained) either due to ineligibility or because the patient declined to participate.

6.4 Interventions

Women fulfilling the eligibility criteria will be randomized to automated insulin delivery (CamAPS FX AiD) or to continue their standard insulin delivery (includes sensor augmented pumps and/or hybrid closed-loop systems other than CamAPS FX, standard insulin pump or MDI), with CGM but without (CamAPS FX AiD). The trial will take place within the home and NHS antenatal clinical settings.

6.4.1 Treatment Arm

6.4.1.1 Products

The automated insulin delivery (AiD) system consists of three separate devices:

- A CE marked subcutaneous insulin infusion pump (**Dana Diabecare R or Dana Diabecare RS [or similar/upgrade]**). Short acting insulins Aspart (Novo Nordisk, Bagsvaerd, Denmark) or Lispro (Eli Lilly, Indiana, USA) are recommended, however, any short-acting insulin may be used in the insulin pump.
- A CE marked continuous glucose monitor (CGM) (**Dexcom G6**). A real-time CGM system based on a subcutaneous glucose sensor recently CE marked for use in pregnant women.
- A CE marked computer-based model predictive control (MPC) algorithm which will compute information from the real-time CGM into a recommended insulin dose and which has been validated during pregnancy (**CamAPS FX**). This will be uploaded onto a mobile phone.

The (previously) investigational device (**CamAPS FX**) is a follow-up of the Florence prototype closed-loop system manufactured by the Cambridge University Hospitals NHS Foundation Trust, used in previous type 1 diabetes pregnancy studies (10-12).

6.4.1.2 Accountability

The investigator will ensure that adequate training is provided by the study team for the study participants and will make every effort, through regular contact, to ascertain that the closed-loop system is used for the study purposes only.

The AiD algorithm will be provided to participants by the study team for the duration of trial participation, with the study team being responsible for ensuring that access to the study-linked AiD algorithm is removed when the participant has completed the study and has been safely transitioned (either off the system, or to a CamAPS commercial account). Participants will be able to keep the insulin pump and remaining CGM devices (sensors and transmitter). NHS support for future use of closed-loop or these individual components, including ongoing provision of pump consumables and CGM sensors will need to be agreed with the participant's clinical team as part of standard clinical care.

6.4.1.3 Treatment Schedule

Patients randomized to the AiD arm will receive training in the following:

- Continuous Glucose Monitoring (CGM) system (To include the same as section 6.4.2.3 below).
- Insulin pump
- Closed-Loop AiD system

Face-to-face or virtual training may be provided at the hospital or outside of the hospital environment at a mutually convenient location e.g. patient's home. CGM training modules (non-trial specific) are available at https://abcd.care/dtn-education/diabetes-tech-in-pregnancy and can be accessed by trial participants and staff. Following completion of the training (prior to 16 weeks gestation) the educator (Study educator or site delegated nurse educator) will ascertain that all areas of training have been covered, including signposting to online CGM and CAMAPS training materials. If competency in the use of the system is not demonstrated, then further training may be provided.

Once competency in the use of the AiD system is demonstrated, participants will proceed to use the system throughout pregnancy, and for up to 6 months post-partum if they wish to do so. The CGM sensor will need to be replaced every 10 days and the CGM transmitter approximately every 3 months. The insulin pump catheter will need to be replaced every 2-3 days. If participants lose the ability to access the CGM data during the trial they should revert to previous methods of capillary glucose monitoring using their own glucose meter.

The CGM glucose measures will be reviewed at study visits during pregnancy, and at 8-12 weeks and 24 weeks post-partum. As CGM data is uploaded in real-time, measures may also reviewed by the clinical care and research teams at any time.

Support and telephone advice will be provided by the research team to deal with any concerns which arise from using the system.

6.4.1.4 Closed-Loop in hospital settings and at end of study procedures

Information will be provided to support NHS staff caring for participants using automated insulin delivery during antenatal hospital admissions, including for antenatal steroids, and during the peri-partum period. If satisfactory glucose control is not maintained women will be transferred to variable rate intravenous insulin infusion aiming to maintain CGM glucose levels between 3.5-7.8 mmol/L during antenatal admissions and delivery. Closed loop should be turned off AUTO mode whilst VRIII is active.

After delivery the CGM target range is 3.9-10.0 mmol/L and participants will continue to use closed-loop for 6 months post-partum. At trial completion, the data from the devices will be checked, and the study-linked CamAPS FX discontinued. Participants will be transitioned onto post-partum insulin therapy by the usual diabetes clinical care team.

6.4.2 Control Arm

6.4.2.1 Products

Participants randomized to the control arm will be provided with the same study CGM device as the intervention group and will use this alongside their normal insulin delivery system using either an insulin pump or MDI (including sensor augmented pumps and/or hybrid closed-loop systems other than CamAPS FX). Participants will use either their own smartphone (if compatible with the CGM

software) or will be provided with a receiver or smartphone (if available) to enable them to view their CGM data in real time. The CGM sensor will need to be replaced every 10 days. The CGM glucose measures will be reviewed at study visits during pregnancy, and at 8-12 weeks and 24 weeks post-partum. As CGM data is uploaded in real-time, measures may also reviewed by the clinical care and research teams at any time.

6.4.2.2 Accountability

The investigator will ensure that adequate training in CGM use is provided by the study team for the study participants.

6.4.2.3 Control Schedule

Participants randomized to the control arm will receive training in the following:

- Continuous Glucose Monitoring (CGM) system. This will include:
    - Insertion and initiation of sensor session
    - CGM Time In Range (TIR) targets and alarm settings
    - Handling real-time CGM feedback including glucose trend arrows, reported high and low glucose
    - Use of software to upload/stream and interpret CGM data

Face-to-face or virtual training may be provided at the hospital or outside of the hospital environment at a mutually convenient location e.g. patient's home. CGM training modules (non-trial specific) are available at https://abcd.care/dtn-education/diabetes-tech-in-pregnancy and can be accessed by trial participants and staff. Following completion of the training (prior to 16 weeks gestation) the educator (Study educator or site delegated nurse educator) will confirm that all areas of training have been covered with the participant, including signposting to online training materials. If competency in the use of the CGM system is not demonstrated, then further training may be provided.

Once competency in the use of the CGM system is demonstrated participants will proceed to use the system throughout pregnancy. The CGM sensor will need to be replaced every 10 days and the CGM transmitter approximately every 3 months. If participants lose the ability to access the CGM data during the trial they should revert to previous methods of capillary glucose monitoring using their own glucose meter.

Support and telephone advice will be provided by the research team to deal with any concerns which arise from using the system.

6.4.3 Dispensing

An initial supply of trial devices will be provided to the study team at each participating centre. Usage of devices will be monitored on a regular basis and additional devices will be provided as appropriate. Devices provided for use in the study should be labelled for use in the AiDAPT trial only.

6.4.4 Compliance and Adherence

In order to ensure that participants can adhere to study procedures, they will be trained in the use of the CGM / AiD closed-loop system and will need to demonstrate that they have the skills required to proceed with the trial. Participants who are unable to do this will be withdrawn from the trial. Participants will also be monitored during standard antenatal visits which will take place either face-

to-face or virtually, at least 4-weekly between 12 weeks until delivery, and at 8-12 weeks and 24 weeks postpartum.

6.4.5 Concomitant Care

Participants in the intervention arm who require medication which significantly affects glucose metabolism (with the exception of prophylactic steroids for fetal lung maturation) should not continue to use the AiD closed-loop system without approval of the Trial Management Group.

6.4.6 Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable adverse device effect or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant
- Significant Clinical Investigation Plan violation or non-compliance
- Allergic reaction to insulin
- Technical problems with the closed-loop system which cannot be resolved
- Any other significant medical event or start of medications that significantly affect glucose metabolism (with the exception of prophylactic steroids for fetal lung maturation)

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up, and data collection and analysis, if they are willing.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome is the percentage of time spent with glucose levels between 3.5-7.8 mmol/L based on CGM levels (TIR 3.5-7.8mmol/L) between 16 weeks gestation and delivery. Data for the intervention group will be collected as part of the data collection from the AiD closed-loop system. Data for the control group will be collected using software provided by the CGM manufacturer.

6.5.2 Secondary Outcomes

6.5.2.1 Maternal Glycaemic Outcomes

1. The time spent with CGM glucose levels above and below target range (TAR>7.8mmol/L, TBR<3.5mmol/L), mean CGM glucose and CGM glucose variability measures (CV, SD).
2. The frequency and severity of hypoglycaemia episodes defined as CGM glucose levels TBR <3.5 mmol/L (level 1 hypoglycaemia) and TBR <3.0 mmol/L (level 2 hypoglycaemia) for at least 15 minutes. Distinct episodes must be separated for at least 30 minutes.

3. The international consensus targets for glycaemic assessment; TIR 3.5-7.8mmol/L >70% (16hr 48 min), TAR >7.8mmol/L <25% (6hr), TBR <3.5mmol/L <4% (1hr), and TBR <3.0mmol/L <1% (15min)
4. The Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) measures
5. Where possible, blood samples will be collected at baseline, 24-26 weeks, 34-36 weeks for HbA1c testing to assess the change in the maternal level. Samples will be stored for further metabolic studies (optional).
6. CGM glucose levels during the first (<12 weeks 6 days gestation), second (13-27 weeks 6 days gestation) and third trimesters (28 weeks until delivery).
7. CGM glucose levels during the 24 hours (midnight to midnight) and overnight time 23.00-07.00hr

6.5.2.2 Maternal Obstetric Outcomes

1. Gestational weight gain (weight gain from booking visit to 36 weeks)
2. Maternal hypertensive disorders (Gestational, worsening of pre-existing hypertension or preeclampsia)
3. Fetal growth (ultrasound estimated fetal weight, head and abdominal circumference measurements)
4. The mode of delivery (vaginal, instrumental, elective caesarean section and emergency caesarean section)
5. The gestational age at delivery and indication for any preterm delivery (<37 weeks)
6. Adverse events including pregnancy loss <24 weeks, stillbirth, neonatal death
7. Maternal hospital admissions (all admissions including the delivery admission)
8. Hospital length of stay (all admissions including the delivery admission)

6.5.2.3. Infant Outcomes

1. Neonatal morbidity including treatment for neonatal hypoglycaemia, neonatal jaundice and respiratory distress between the time of infant delivery and discharge from hospital.
2. Infant birth weight (customised birth weight percentile, incidence of large for gestational age (LGA), and small for gestational age (SGA)
3. Neonatal intensive care unit (NICU) admission >24 hours
4. Infant feeding at hospital discharge, 8-12 weeks postpartum, and 24 weeks postpartum (breast, bottle, both)
5. Hospital length of stay (from delivery until hospital discharge), including re-admissions >24h within the first seven days from birth

6.5.3 Safety Outcomes

1. The frequency and severity of diabetic ketoacidosis during the period of inclusion in the trial
2. The number and severity of episodes of severe hypoglycaemia during the period of inclusion in the trial
3. The number and severity of episodes of adverse device effect

6.5.4 Psychosocial Outcomes

The following questionnaires will be completed at Baseline and 34-36 weeks

1. Insulin Delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) (16)
2. The EQ-5D Health-Related Quality of Life Questionnaire (17)
3. Diabetes Distress Scale (DDS) (18)
4. Hypoglycaemia Fear Survey Questionnaire II (HFSQ II) (Worry scale only) (19)
5. Pittsburgh Sleep Quality Index (PSQI) (20)

Qualitative interviews will be conducted with a smaller sample of trial participants who provide additional consent for a qualitative interview:

1. 25 women randomized to the AiD arm will be interviewed post randomization and again at 34-36 weeks
2. Up to 25 staff from the trial sites will be interviewed

6.5.5 Health economic outcomes

1. Cost of the AiD closed-loop system (cost of the study pump, CGM, and control algorithm). Details of the purchase price and of the use of sensor and pump consumables based on typical or expected usage, will be estimated.

2. Cost of the control-arm glucose monitoring and insulin delivery

3. Training costs for AiD and control arms

4. Maternity health care use for AiD and control arms: this includes
    - NHS antenatal clinic visits
    - Between visit contacts which will be logged and grouped as a) Questions around diabetes management, b) Technical Issues with the devices, c) Questions relating to both 1 and 2 above
    - Antenatal hospital admissions (number and total length of hospital stay) including the delivery admission length of hospital stay
5. Neonatal health care use for AiD and control arms: this includes
    - Costs of delivery vaginally or by caesarean section
    - Costs associated with any complication of delivery, and neonatal complications
    - Neonatal intensive care unit admissions (level of care and duration of admission)
    - Total neonatal length of hospital stay
6. The EQ-5D Health-Related Quality of Life Questionnaire

The cost-effectiveness of the closed loop system will be estimated using the study primary outcome measure of time spent with glucose levels between 3.5-7.8 mmol/L. This cost-effectiveness study will estimate any additional cost per additional week of good glucose control. Additionally, collection of the EQ-5D-5L will enable estimation of quality adjusted life years (QALYs) for a cost-utility analysis.

6.5.6 Post-partum outcomes

Refer to Appendix 1 for details.

6.6 Participant Timeline

	Initial Contact	Recruitment visit	Randomiz-ation visit (Recruitment +1-2 weeks)	Training	Routine antenatal appts (12, 16, 20 weeks)	24-26 weeks	Routine antenatal appts (28 and 32 weeks)	34-36 weeks	Delivery	Hospital discharge (infant)	8-12 weeks post-partum	24 weeks post-partum
PIS given/sent (hard copy or electronic)	X											
Check inclusion / exclusion criteria		X										
Obtain written informed consent		X										
Height and weight, medical history		X										
CGM data collection		CGM sensor inserted at recruitment and anonymised CGM data collected (96 hours)		All participants wear CGM from trial entry. Data streamed continuously via smartphone / automated insulin delivery system or uploaded at each visit via receiver								
Questionnaires		X	(confirm all completed)					X				
Blood sample collection (5 mL) for future metabolic studies (where			X			X		X				
HbA1c level (where possible)			X*			X		X				
Fetal growth† (where available from routine ultrasound scans)					X (20 wks only)		X	X				
Average total daily dose insulin during past 3 days		X	X		X	X	X	X	X		X	X
Randomization			X									
Training and competency evaluation			Post-randomization, must be completed by 15wk 6d									
! Routine visit data collection					X	X	X	X				
Adverse event collection		All Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs), Device deficiencies which may have resulted in a SADE and Unanticipated Serious Adverse Device Effects (USADEs) must be reported to NCTU in line with section 7									
Qualitative interviews (select participants)		X						X				
Participant descriptive feedback											X	X
!! Data Collection at Delivery									X			
# Infant Care and Feeding Data										X	X (feeding data only)	X (feeding data only)

† Fetal growth scan data (head circumference, abdominal circumference and estimated fetal weight) will be collected where available from routine ultrasound scans at approximately 20, 28, 32 and 36 weeks

! Maternal weight, insulin delivery method, total insulin dose, medication use, study contacts, hospital admission, skin assessment, episodes of severe hypoglycaemia, episodes of diabetic ketoacidosis, adverse events, device deficiencies.

!! Delivery data - antenatal corticosteroids, insulin delivery method, method of infant delivery (vaginal or caesarean), episodes of severe hypoglycaemia, infant birthweight, sex and gestational age, birth injury, length of hospital stay until first discharge home.

Infant data - High level neonatal care >24 hours, length of NICU stay, neonatal hypoglycaemia treated with buccal mucosa 40% glucose gel and/or iv dextrose, neonatal hyperbilirubinemia, respiratory distress, length of hospital stay until first discharge home.

* HbA1c repeated at randomization to confirm eligibility if >10% [86 mmol/mol] previously. A CGM or Libre GMI (glucose management indicator) may also be used to confirm eligibility if GMI >86 mmol/mol (>10%) previously.

6.6.1 Patient Assessments

The following will be undertaken:

6.6.1.1 Recruitment visit (Between ultrasound confirmation of viable pregnancy and 13 weeks and 6 days gestation)

When women have agreed to participate, they will be invited for the recruitment visit, when the following activities will be performed by the research team:

- checking for inclusion and exclusion criteria
- written informed consent
- past medical (diabetes and obstetric) history
- body weight and height, calculation of BMI
- baseline questionnaire pack provided for participants to complete at home (either paper or electronically via link)
- Dexcom G6 sensor insertion
    - For **women not already using Dexcom G6**, a Dexcom G6 subcutaneous glucose sensor will be inserted by the clinical research team and the participant will be instructed to wear it at home for 10 days with a receiver device. They will be asked to return the receiver for uploading of their anonymised baseline CGM data within 14 days.
    - **Women who are already using Dexcom G6** will have a new Dexcom G6 glucose sensor inserted and either given a receiver device as above or switched from their personal Dexcom account to an anonymised study Dexcom account on their smartphone.

6.6.1.2 Randomization Visit (Up to 15 weeks and 6 days gestation)

The following activities will be performed:

- CGM sensor upload from receiver / CGM data review
- Baseline bloods (where possible)
- Collection / confirmation of the completed baseline questionnaires
- Confirm HbA1c or GMI level ≤ 86mmol/mol (10%)
- Record average total daily dose (TDD) of insulin during the previous 3 days
- Randomization via study website
- Participant training and/or schedule participant training visit(s)

The CGM sensor data will be downloaded from the receiver by the research team / reviewed via the study account to provide a baseline glucose control assessment. At least 96 hours of CGM glucose values with 24 hours of glucose values during the hours of 11pm and 7am are required. If there are technical difficulties and/or inadequate CGM data a second CGM sensor will be provided (if possible within the required timeframes for visits). The CGM readings recorded during this period will also be used to optimise insulin therapy in both groups.

If laboratory measurement of HbA1c levels are unavailable (e.g. due to COVID-19 regulations), estimates from Glucose Management Indicator (GMI) in Libre/CGM are acceptable.

6.6.1.3 Participant Training – Intervention Arm

(Post-randomization visit, within a maximum of 15 weeks and 6 days weeks gestation)

The device training for existing pump users randomized to AiD may take up to 120 minutes but, may need an additional 90-120 minutes for users who do not have pump experience. The training can either be performed at one or more than one session, according to the participant's past device experience and preference, and may take place face-to-face or virtually at a mutually convenient location e.g. outpatient clinic or patient's home.

A 'top tips' guidance leaflet for using the pump and closed loop system will be provided for reference. Training modules are available at https://camdiab.cdep.org.uk/ for trial participants and staff to access.

6.6.1.3.1 CGM training (30-60 minutes)
CGM Training can be commenced at the randomization visit, completed in full at the randomization visit or rescheduled at the participant's convenience (as long as it is possible for all device training to be completed by 15 weeks and 6 days gestation),

Women will be trained by the clinical research team to insert a subcutaneous glucose sensor and will be provided with the study CGM system to wear at home until they are confident with using the device and interpreting CGM data.

6.6.1.3.2 Study pump training (up to 240 minutes)
Women will be switched from their regular intensive insulin regimen (insulin pump or MDI) to the study insulin pump. Insulin pump training may take 30-60 minutes for women with pump experience. For women with no previous pump experience randomized to closed-loop it is expected that the insulin pump training may require up to 180-240 minutes, to ensure participant's safety during both automated and manual pump modes. The device training can be split over 2 visits, starting with CGM training before the study pump/closed-loop training session.

Women will be given training on the functionality of the study pump by the research team and provided with the insulin pump user manual. For women already using insulin pump therapy their usual pre-meal insulin: carbohydrate ratios and insulin sensitivity /correction factors will be programmed into the bolus calculator in the study insulin pump.

For women transferring from multiple daily injections (MDI), CSII conversion will be standardised to 70±10% of the MDI total daily insulin dose starting at a flat basal rate representing 50% TDD. Their pre-meal insulin: carbohydrate ratios and insulin sensitivity /correction factors will be provided by the research team. Women will be advised to use the bolus calculator for all insulin boluses when 10 gram or more of carbohydrate are consumed.

Women with no previous insulin pump experience may decide whether to start both study pump and closed-loop at the same time as the CGM or to start the CGM alone (as long as it is possible for all device training to be completed by 15 weeks and 6 days gestation) before starting the insulin pump and closed-loop system. All training contacts will be documented in the clinical report forms.

6.6.1.3.3 Closed-loop training (30 minutes)
A demonstration session on the use of the automated closed-loop system will be provided at the same time as the insulin pump training so that participants are confident using the study pump in

both manual and automated modes. This will include how to start and stop the AiD system, responding to alarms and trouble shooting.

The diabetes educator will check that the closed-loop system is working together as expected prior to the participant leaving the training session.

6.6.1.4 Participant Training – Control Arm (up to 120 minutes) (Randomization + up to 14 days with a maximum of 15 weeks and 6 days gestation)

An equivalent 2-hour training session will be provided for control group participants on subcutaneous glucose sensor insertion, CGM data interpretation (60 minutes), dietary advice and insulin dose adjustment (60 minutes). A 'top tips' guidance leaflet for using the Dexcom G6 CGM will be provided for reference. Personalised insulin dose adjustment algorithms will be provided to insulin pump and MDI users in the control arm. As per the intervention group session, this can be commenced (CGM training) or completed (CGM and insulin dose adjustment) and at the randomization visit, or rescheduled at the participant's convenience and may take place face-to-face or virtually at a mutually convenient location e.g. outpatient clinic or patient's home. CGM training modules for trial participants and staff are available at https://abcd.care/dtn-education/diabetes-tech-in-pregnancy.

6.6.1.5 Competency Assessment (Up to 15 weeks and 6 days gestation)

Competency to use CGM / AiD will be assessed by the research team to ensure women have the skills and confidence required to proceed with those devices. They must demonstrate competence in sensor insertion (all participants), and in the technical management of the study insulin pump during manual and AiD modes (intervention participants). If competency and/or compliance are suboptimal in any aspect, further training will be provided. Specifically, a further 7-14 day home trial will be allowed, after which competency and compliance will be re-assessed. If, at the end of this second training session, women are unable to fulfil the competency and/or compliance criteria, their withdrawal from the study will be considered.

6.6.1.6 Procedures following training

Once participants have completed the training, they will proceed to use CGM / AiD throughout pregnancy, and for 6 months after delivery. Participants in the control arm will continue to use current methods of delivering insulin. The study CGM sensors will be used from recruitment until 6 months after delivery to provide comparable outcome data collection in accordance with the study schedule.

6.6.1.7 Study visits

It is expected that the majority of ongoing study visits will coincide with routine NHS antenatal clinic visits, which will occur at least 4-weekly from 12-36 weeks (12/40, 16/40, 20/40, 24/40, 28/40, 32/40, 36/40, 38/40) until delivery. However, due to the ongoing COVID-19 regulations, virtual study visits (e.g. using video calls or telephone appointments) will be offered as an option to minimise face-to-face contacts. After delivery a telephone, video-call or in-person visit will be held at 8-12 and at 24 weeks.

At these visits the following data will be recorded on the study database:

- Weight (during pregnancy)
- Blood Pressure (during pregnancy)
- Insulin dose and type
- Adverse events noted during skin assessment
- Details of any issues with devices
- Details of all adverse events

6.6.1.8 Outcome assessments

The following activities will be performed at 24-26 and/or at 34-36 weeks

- Blood collection at 24-26 and at 34-36 weeks, where possible (for future metabolic research studies and HbA1c levels)
- Follow-up questionnaires and qualitative interviews at 34-36 weeks
- Weight
- Blood Pressure
- Insulin dose and type
- Adverse events noted during skin assessment
- Details of any issues with devices
- Details of all adverse events

Fetal biometry data will be recorded, if available from routine ultrasound scans performed at around 20, 28, 32 and 36 week visits:

- Fetal head circumference, abdominal circumference and estimated fetal weight

Participants who have withdrawn from AiD, and who are still happy for their data to be collected, will be asked to continue CGM use as per the control group.

6.6.1.9 Procedures at delivery

Written procedures will be provided to site staff to cover actions required at delivery. The following obstetric and neonatal outcomes will be collected:

1. Mode of delivery (vaginal, instrumental, elective caesarean section and emergency caesarean section)
2. Gestational age at delivery and indication for any preterm delivery <37 weeks
3. Infant(s) birth weight (customised birth weight percentile, incidence of large for gestational age (LGA), and small for gestational age (SGA)
4. Neonatal morbidity (treatment for neonatal hypoglycaemia, neonatal jaundice, respiratory distress)
5. Neonatal care admission (duration of stay, highest level care)
6. Adverse events (pregnancy loss <24 weeks, stillbirth, neonatal death)
7. Infant(s) feeding at hospital discharge (breast, bottle, both)

6.6.1.10 Post-partum

After delivery, and prior to maternal hospital discharge, the post-partum glucose targets will be applied 3.9-10.0 mmol/L. Consenting participants will continue with their randomised treatment allocation (standard care with CGM, or closed-loop intervention) for six months following delivery.

6.6.1.10 Neonatal readmissions

In cases of neonatal readmissions where the infant requires readmission within the first 7 days of life, (e.g. for neonatal hyperbilirubinemia see section 9, outcome definitions) the data will be collected in the CRF.

6.6.1.11 Early pregnancy loss

In the event of early pregnancy loss in a participant on the intervention arm, the participant should be asked to return the study devices to the research team (via arranged post if this is more convenient for the participant), or the study-linked CamAPS FX app removed at the earliest suitable opportunity . If necessary, the study CamAPS FX app can be continued for a period to enable safe transition onto standard insulin therapy by the usual diabetes clinical care team. We expect usual insulin therapy to be resumed within 6-8 weeks; any instances greater than 8 weeks should be discussed with the Trial Management Group.

6.6.2 Questionnaires

Participants will be asked to complete the following questionnaires at baseline and again at 34-36 weeks:

1. The INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) questionnaire (intervention group only).
2. The EQ-5D Health-Related Quality of Life Questionnaire
3. The Diabetes Distress Scale (DDS)
4. The Hypoglycaemia Fear Survey Questionnaire II (HFSQ II) (Worry scale only)
5. Pittsburgh Sleep Quality Index (PSQI)

These can be completed in participants' own homes and returned prior to randomization.

The INSPIRE questionnaire assesses psychosocial aspects of technology including expectations, psychosocial functioning, impact on self-management, impact on health, usability, wearability and burden (16). Items are scored on a 5-point scale from 'strongly agree' through 'strongly disagree'. Specific questions are asked to address regulatory approvals and concerns around managing AiD expectations. It is applicable only to the intervention group.

The EQ-5D Health-Related Quality of Life Questionnaire (17) is a self-rated health status using a visual analogue scale. It provides a self-reported description of current health in 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The concept of health in EQ-5D also encompasses both positive aspects (well-being) and negative aspects (illness). The utility score is an expression of the Quality Adjusted Life Years (QALY).

The Diabetes Distress Scale (DDS) assesses worries and concerns specifically related to diabetes and its management; it has been shown to be a good marker of factors important to diabetes-related quality of life and has good reliability (alpha ≥0.87) and validity (18). The newer DDS for T1D includes 17 items. Responses are rated on a 6-point scale from 'not a problem' to 'a very serious

problem'. Four sub-domains, in addition to a total score, provide detailed assessments of emotional burden, physician-related distress, regimen-related distress, and diabetes-related interpersonal distress.

The Hypoglycaemia Fear Survey Questionnaire is a validated questionnaire to measure several dimensions of fear of hypoglycaemia (19). The modified questionnaire to be used within this trial consists of a 13-item "Worry subscale" that measures anxiety and fear surrounding hypoglycaemia.

The PSQI (20) is a validated 19-item questionnaire that holistically assesses sleep quality and sleep duration over the preceding month.

At around 8-12 weeks and 24 weeks post-partum, participants will be invited to provide feedback about their experiences on the trial through free text descriptive writing. Full details can be found in Appendix 1.

6.6.3 Blood Sampling

COVID-19 has severely restricted the access and the laboratory capacity of sites. Therefore although baseline HbA1c levels should ideally be measured from blood samples, GMI estimates from Libre or CGM devices are allowable at sites. In addition, less than 5 ml of whole blood will be taken from each participant to be stored for subsequent metabolic studies, where possible.

A sample handling Work Instruction will be provided to all sites detailing sample collection and handling procedures. All samples taken will initially be stored at sites and will then be transferred to the Norwich Biorepository for storage prior to analysis. Detailed written instructions and appropriate tissue transfer agreements will be put in place prior to the transfer of relevant material.

6.6.4 Qualitative interviews

Women randomized to AiD will be interviewed as soon as possible post-randomization to enable their pre-trial diabetes management practices, everyday work and family lives, and their initial expectations of using AiD technology to be captured and explored in-depth. The same participants will be followed-up at approximately 34-36 weeks gestation to look at whether, in what ways, and why, AiD use has impacted of their diabetes self-management practices, pregnancy experiences and work and family lives.

Approximately 25 women will take part in the interviews, recruited from across the trial sites. Women will be purposively sampled to capture diversity in terms of age, education, socio-economic status, previous pregnancies, diabetes duration and baseline HbA1c.

These interviews will also explore how women think the technology could be refined in light of their experiences of using it during pregnancy. The follow-up interviews have been timed to coincide with collection of clinical and psychological data at 34-36 weeks gestation to aid interpretation of these data.

20-25 site staff sampled to reflect diversity in terms of clinical and trial experience will also be interviewed at, or near to, close-out of the trial. By this time, they will have a diversity of experiences of delivering the trial, and supporting pregnant women who have used closed-loop systems, upon which they can draw.

6.6.5 Early Stopping of Follow-up

If a participant chooses to discontinue their trial intervention, they should continue to be followed up as closely as possible to the follow-up schedule defined in the Clinical Investigation Plan, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the allocated trial intervention. Should they choose to withdraw from the intervention only, they will be asked if would like to continue to provide outcome data (CGM data, delivery/neonatal/post-partum data and questionnaire data). If, however, the participant exercises the view that they no longer wish to be followed up, this view must be respected and the participant withdrawn entirely from the trial. NCTU should be informed of the level of withdrawal via the study database. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants on the intervention arm who do not wish to continue with AiD should return the study phone to the research team to enable the algorithm to be removed.

Participants who fail to complete training and participants in both arms who stop trial follow-up early will be monitored.

6.6.6 Participant Transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

Participants who deliver their babies at another centre or whose babies are in NICU at another centre should be followed up by the original consenting centre. Instructions will be provided which can be passed to non-study centres to ensure that the standard guidelines for glucose management at delivery are followed.

6.6.7 Loss to Follow-up

Participants will be in contact with the clinical care team at 4-weekly intervals during the trial, or more frequently if clinically indicated. Loss to follow-up is therefore anticipated to be minimal for this study.

6.6.8 Trial Closure

The end of the trial is defined as 6 months following the last follow-up visit of the last patient, to allow for data entry and data cleaning activities to be completed.

6.7 Sample Size

The power calculations aim to compare the effect of closed-loop on the time spent in the target glucose range (CGM TIR 3.5-7.8mmol/L) and are based on data from our previous studies of CGM and closed-loop in pregnancy (CONCEPTT and CLIP_03) (10, 21). During the pregnancy arm of CONCEPTT (an RCT of CGM in T1D pregnancy) women spent 52%±14% TIR 3.5-7.8mmol/L at baseline (12±2 weeks), 50% ±13% TIR 3.5-7.8mmol/L at 24±2 weeks and 63%±15% TIR 3.5-7.8mmol/L at 34 weeks gestation. To detect a 10% absolute difference the time spent in the CGM target glucose range TIR 3.5-7.8mmol/L (equivalent to an extra 2.4 hours/day) between automated closed-loop and standard insulin delivery, 98 participants are needed to achieve 90% power and an alpha level of

0.05 (two-tailed). The standard deviation of the primary efficacy outcome is 15% as observed in CONCEPTT. We anticipate 10% pregnancy loss and 10% of randomized participants who withdraw, which takes the total sample size to n=124 (62 per arm) participants randomized.

6.8 Recruitment and Retention

6.8.1 Recruitment

Potential participants will be identified by their treating clinicians, provided with study information leaflets and invited to join the study prior to the recruitment visit. They may also contact the clinical research team directly. All women will be offered the opportunity to discuss the pros and cons of study participation with a member of the research team and/or their diabetes/obstetric physician/obstetrician. Participants will only be consented to the study once a viable pregnancy has been confirmed using ultrasound.

6.8.2 Retention

Participants will remain in the trial for the duration of their pregnancy and following delivery if they wish to continue with the trial, until 6 months post-partum. During pregnancy, participants will be seen by the clinical research team on at least a 4-weekly basis.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

Eligible participants will be randomized via a web-based randomization system. Women will be allocated as they are enrolled with stratification per study site. They will be allocated on a 1:1 basis to either the intervention arm (automated insulin delivery system (insulin pump, CGM and phone)) or control arm (patient directed insulin delivery (insulin pump or MDI) and CGM without AiD).

6.9.1.2 Allocation concealment mechanism

The allocation is computer generated so will not be known prior to the participant being randomized. The patient will be allocated a participant number at time of consent. When and all pre-designated questions have been completed in the CRF, the research staff will have access to the randomization process for that participant. The treatment allocation will be revealed and linked to that participant number. Allocation is concealed prior to randomization to prevent treatment bias.

6.9.1.3 Allocation Implementation

Eligible subjects will be randomized using central randomization software to the automated or standard insulin delivery. The randomisation will be stratified at each centre.

6.9.2 Blinding

This is an unblinded trial. Both participants and their clinical care team will be aware of the allocation.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique trial Participant IDentification Number (PID). Data will be collected at the time-points indicated in section 6.6.

The preferred method of data collection is direct online entry of data onto the central database, stored on servers based at the Jaeb Center for Health Research, by members of the AiDAPT trial team working

within each research site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not an essential step). Staff will receive training on data collection and use of the online system.

Safety data and other data requiring expedited reporting will be reported directly to NCTU via email using supplied paper CRFs in accordance with section 7.

Data collection, data entry and queries raised by a member of the AiDAPT trial team will be conducted in line with the NCTU and trial specific Data Management Standard Operating Procedure.

Identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room.

Clinical trial team members will receive trial Clinical Investigation Plan training. All data will be handled in accordance with the General Data Protection Regulation (GDPR) (EU) 2016/679 and the Data Protection Act 2018.

6.10.2 Data Management

Data will be entered under the participants PID number onto the central database stored on the servers based at Jaeb. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the AiDAPT trial teams at Jaeb and NCTU, and external regulators if requested.

The database and associated code have been developed by the Jaeb Center for Health Research, in conjunction with the AiDAPT trial team. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised PID, will be held locally by the trial site. This will either be held in written form in a location secured against unauthorized access or electronically in appropriately protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by the Sponsor.

6.10.3 Non-Adherence and Non-Retention

Every effort will be made to record the reasons for non-adherence (e.g. discontinuation of intervention due to harms or lack of efficacy) and non-retention (i.e. consent withdrawn; loss to follow up) as this information can influence the handling of missing data and interpretation of results.

6.10.4 Statistical Methods

6.10.4.1 Primary Outcome Analysis

The primary analysis will evaluate the change in the time spent in the target glucose range (CGM TIR 3.5-7.8 mmol/l) between the intervention and control arm between 16 weeks gestation and delivery.

6.10.4.2 Secondary Outcome Analyses

6.10.4.2.1 Key secondary endpoints

- Overnight (23.00-07.00hr) percentage time in target range (TIR 3.5-7.8mmol/L)
- Percentage time above target (TAR > 7.8 mmol/l)

6.10.4.2.2 Other secondary endpoints

- HbA1c and average CGM glucose to quantify glucose control
- Proportion of participants achieving the international consensus targets for CGM glycaemic assessment; TIR 3.5-7.8mmol/L >70% (16hr 48 min), TAR >7.8mmol/L <25% (6hr), TBR <3.5mmol/L <4% (1hr), and TBR <3.0mmol/L <1% (15min)
- Percentage time spent at CGM ≥3.5 to ≤10.0 mmol/l to quantify near optimal target range
- Percentage time spent with CGM <3.5 mmol/l to quantify borderline hypoglycaemia
- Percentage time spent with CGM <3.0 mmol/l to quantify moderate hypoglycaemia
- Percentage time spent at CGM >10.0 mmol/l to quantify hyperglycaemia
- Area under the curve (AUC) for blood sugars:
    - >7.8 mmol/l
    - >6.7 mmol/l
    - <3.5 mmol/l
    - <3.0 mmol/l
- Low Blood Glucose Index (LBGI) to quantify the risk of hypoglycaemia
- Standard deviation (SD) of CGM glucose to quantify the glucose variability
- Coefficient of variation (CV), of CGM glucose to quantify the glucose variability
- Insulin delivered (basal, bolus, and total) to assess insulin needs
- Mild-moderate episodes of hypoglycaemia <3.5 (level 1) and <3.0 (level 2) from CGM data defined as AUC <3.5 or AUC ≤3.0 for 15 minutes duration
- Nocturnal hypoglycaemia (NH): CGM glucose <3.5 (level 1) and <3.0 (level 2) between 23:00 and 07:00 hours

The 24hr (midnight to midnight) and overnight time (23.00-07.00hr) periods will be assessed separately (for percentage TIR 3.5-7.8mmol/L, average CGM glucose, percentage TAR, percentage TBR, and glucose variability measures (SD,CV).

Group difference of above secondary outcomes [percentage time in target range, mean CGM glucose, percentage time above target, percentage time below target, and glucose variability measures (SD,CV)] will be assessed separately for the first trimester (<12 weeks 6 days gestation), second trimester (13-27 weeks 6 days gestation) and third trimesters (28 weeks until delivery).

Group difference in final maternal obstetric outcomes and infant outcomes will also be assessed. Maternal obstetric outcomes include gestational weight gain, maternal hypertensive disorders, mode of delivery, gestational age, adverse events (pregnancy loss, stillbirth, neonatal death), number of maternal hospital admissions and hospital length of stay. Infant outcomes include neonatal morbidity, infant birth weight, NICU admission, infant feeding and hospital length of stay.

6.10.4.3 Safety Evaluation

Safety data including number and severity of diabetic ketoacidosis, severe hypoglycaemia and episode of adverse device effects will be tabulated for all subjects, including drop-outs and withdrawals, irrespective of whether CGM data are available and irrespective of whether closed-loop was operational. Severe hypoglycaemia events will be defined as events requiring assistance of another person actively to administer carbohydrate, glucagon or other resuscitative actions.

6.10.4.4 Patient Reported Outcome Measures (PROMS) Evaluation

Descriptive tabulations of questionnaires will be carried out, and scores will be calculated using providing scaling and scoring tools as appropriate. The between group difference of each score at 34-36 weeks will be assessed.

6.10.4.5 Statistical Analysis

Means ± SD values or percentiles appropriate to the distribution will be reported for the primary outcome and secondary glycaemic control/insulin outcomes by treatment group at baseline and intervention period.

A linear mixed effects regression model will be fit with time in range from 16 weeks gestation until delivery as the dependent variable adjusting for baseline time in range, insulin delivery modality (pump vs MDI) at baseline and clinical centre and subject as random effects. Note that the random subject effects will account for correlated data if some participants are enrolled for multiple pregnancies. A point estimate, 95% confidence interval and p-value will be reported for the treatment effect based on the linear regression model. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or robust statistical methods will be used instead.

For secondary glycaemic control/insulin outcomes, similar models as described above will be used. A p-value which shows the effect for each outcome will be reported. Linear regression models will be used to compare continuous outcomes between treatment groups by adjusting for corresponding metric calculated at baseline, baseline insulin delivery modality and clinical centre as random effect. Generalized linear mixed effects models will be used to compare CGM measured episodes of hypoglycaemia.

Selected CGM outcomes (mean CGM glucose, time in, above and below range, glucose SD and CV) will be calculated for the overnight period (23.00-07.00hrs). These same selected CGM outcomes will also be calculated for the 1^{st}, 2^{nd} and 3^{rd} trimesters separately, similar linear models as described above will be used to compare the between group differences.

For assessing group difference in maternal obstetric outcomes, infant outcomes and safety outcomes, linear regression models will be used to compare continuous and ordinal variables, logistic regression will be used to compare categorical variables, and Poisson regression models will be used to compare event rates, while adjusting for insulin delivery modality at baseline and random site effect. For analysis of adverse events, formal statistical comparisons will only be performed when there are enough observed events.

For assessing group difference in questionnaire data at 34-36 weeks, linear regression models will be fit while adjusting for corresponding baseline scores, insulin delivery modality at baseline and clinical centre.

Missing data for the primary outcome will be handled using multiple imputation with pattern mixture models assuming the dropout trajectory of the treatment subjects was that of the control arm. Missing data for secondary outcomes will not be imputed.

Since HbA1c measurements are optional due to the COVID pandemic there may be a large number of missing values. GMI values will not be used to substitute for missing HbA1c measurements (note that GMI is a linear shift of mean glucose which is a separate outcome listed above). The method of direct likelihood will be used to handle missing HbA1c values.

Primary analysis consists of a single comparison of time in range over pregnancy as described above. Two sided p-value will be reported and a 5% significance level will be used to declare statistical significance. For all above mentioned secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

A detailed statistical analysis plan will be drafted and approved by the Data Monitoring Group prior to data lock.

6.10.4.6 Subgroup Analyses

The study is not powered to detect subgroup differences. Interpretation of any subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. In the absence of such an overall difference and if performed, the following subgroup analyses will be conducted for the primary outcome and will be interpreted with caution: (1) insulin delivery modality (pump vs MDI) at baseline, (2) baseline HbA1c (<7.5% vs ≥7.5%), (3) maternal age, and (4) clinical centre. This analysis will be carried out through the use of an interaction term in the analytical models.

Participants missing any baseline values will be excluded from the corresponding subgroup analysis. GMI will not be used to impute any missing baseline HbA1c values

6.10.4.7 Additional Analyses

6.10.4.7.1 Functional Data Analyses

Functional data analyses will also be used to evaluate temporal trends in CGM data between the interventions. Functional data analyses techniques allow us to extract shape information and identify patterns that are not identified by more commonly used summary statistical measures when analysing complex data from frequent sampling. It yields quantifiable measures (of absolute values over time, velocity and acceleration) and allows physiological interpretation of the data accounting for their complexity of the temporal character. It can be used to summarise temporal trends in continuously recorded measurements in a form that is amenable to subsequent multivariable statistical analysis.

Multivariable regression of summary statistical indices and FDA of CGM data will be used to assess the relationship between glucose in each trimester of pregnancy and neonatal birthweight measures after adjustment for confounding.

6.10.4.7.2 Closed Loop System Use Assessment

In the AiD arm, the percentage of time CGM is used, and when closed-loop is active, will be calculated on a 4-weekly basis and for the overall treatment period. For the control group, the percentage of time CGM is used will be calculated on a 4-weekly basis and for the overall treatment period.

6.10.4.7.3 Device Issues

The frequency for different types of device issues will be summarized for both treatment groups. Listing of all device effects will be reported by clinical centre and treatment group.

6.10.4.7.4 Exploratory Analyses

An exploratory analysis of the relationship between fetal growth and maternal glycaemia will be performed.

Additional exploratory analyses will be performed on post-partum glycaemia and insulin doses – see Appendix 1 for details.

6.10.4.8 Analysis Population

The analyses will follow the intention-to-treat principle. It will include all randomized participants, the data from whom will be analysed in the group to which the subjects were assigned through randomization regardless of the actual treatment received. Data will not be truncated due to protocol deviations.

6.10.4.9 Sensitivity Analysis

6.10.4.9.1 Per-Protocol Analysis

A per-protocol analysis will be performed on the subjects who meet the following criteria if at least 10% of the sample will be excluded:

- Participants who complete the 34-36 week visit
- Minimum of 96 hours CGM data
- Intervention arm: closed-loop active for at least 60% of the time

6.10.4.9.2 Sensitivity Analysis for Multiple Pregnancies

Sensitivity analysis for the primary outcome will be performed to assess impact of including only a participants first pregnancy in the analysis. A linear regression model will be fit with time in range from 16 weeks gestation until delivery as the dependent variable adjusting for baseline time in range, insulin delivery modality (pump vs MDI) at baseline and clinical centre as random effect.

6.10.4.9.3 Confounding

A sensitivity analysis will also be conducted for the primary endpoint if potential confounding factors collected at baseline will be detected.

6.10.4.9.4 Missing Data

Following alternative approaches will be used for handling missing data for the primary endpoint:

- Direct likelihood method
- Rubin's multiple imputation with treatment group in the imputation model

6.10.5 Within-trial analysis

A separate health economic analysis plan will be drafted and approved by the Trial Management Group before commencement of the within-trial economic evaluation

6.10.6 Analysis of Qualitative Information

Interviews will be digitally recorded and transcribed. To maximise rigor, several team members will be involved in data analysis, with clinical input from local site investigators, obstetrics (FD) and diabetes (HM). A thematic analysis will be undertaken (Strauss & Corbin, 1990) by these individuals who will independently review all data before attending regular meetings to compare their interpretations and reach agreement on recurrent themes and findings.

Each woman's baseline and follow-up interview will be compared, and attention paid to any continuities and changes in their attitudes, experiences and self-management practices over time, and the reasons for these. Participants' accounts will also cross-compared, enabling the identification of overarching themes and discrepant views (e.g. between staff and women).

A final coding frame, reflecting the initial research questions and emergent themes, will be developed once all data have been reviewed and consensus reached on key themes and findings. NVivo9, a qualitative software package, will be used to facilitate data coding/retrieval.

6.10.7 Analysis of Tissue Samples

Where possible, blood samples will be taken at 3 collection points to allow measurement of HbA1c levels.

In addition, an optional sample of up to 4mL of plasma from each of the three collection points will be stored at minus 80°C for use in future metabolic studies. Testing undertaken on these studies will be determined by the TMG at a future date based on current knowledge at the point the samples are analysed.

A laboratory manual will be developed and agreed by the TMG prior to any analysis of samples.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

Further details of the roles and responsibilities of the Data Monitoring Committee (DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the AiDAPT DMC Terms of Reference (ToR).

6.11.2 Interim Analyses

There will be no formal interim analyses however safety outcomes will be reviewed by the research team monthly, by the DMC and trial steering committee every 6 months. The DMC will be informed of any maternal or perinatal death within 7 days.

6.11.3 Data Monitoring for Harm

Adverse events will be collected at each visit and analysed according to the Statistical Analysis Plan. Adverse events by treatment group will be reviewed regularly by the Data Monitoring Committee as described in their terms of reference.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the AiDAPT trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central Monitoring at NCTU

NCTU staff will review electronic Case Report Form (eCRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the trial Data Management Plan.

6.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the AiDAPT Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this will obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the Clinical Investigation Plan. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the AiDAPT Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TT terms of reference.

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Trial Steering Committee

The Trial Steering Committee (TSC) is the group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.11.4.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. When an institution is the trial sponsor and has delegated some and/or the totality of Sponsor's activities to the CI and NCTU, the Sponsor's form for delegated activities should be completed and signed by all parties before the start of the trial.

7 Safety reporting

The following definitions of harm derived from ISO 14155 apply to this trial.

Table 1: Adverse Event and Device Deficiency Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in a participant, whether or not related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved.
Serious Adverse Event (SAE)	Any AE that: • led to death • led to serious deterioration in the health of the subject, that either resulted in a. a life-threatening illness or injury* b. a permanent impairment of a body structure or a body function c. in-patient or prolonged hospitalization** d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • led to fetal distress, fetal death or a congenital abnormality or birth defect.
Adverse Device Effect (ADE)	An Adverse Event related to the use of the investigational medical device. NB: This includes; • AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. • AEs resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Device Effect (SADE)	An Adverse Device Effect which resulted in any of the consequences characteristic of a SAE.
Unanticipated Serious Adverse Device Effect (USADE)	A Serious Adverse Device Effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

	NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.
Device Deficiency	An inadequacy of the trial device with respect to its identity, quality, durability, reliability, safety or performance. This definition includes malfunctions, use errors and inadequate labelling.

* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) or planned hospitalization for a pre-existing condition or a procedure required by the Clinical Investigation Plan without serious deterioration in health do not constitute SAEs.

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial procedures / intervention. (This does not include pre-existing conditions recorded as such at baseline)
- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalization where no untoward or unintended response has occurred e.g. elective cosmetic surgery

7.1 Exempted Serious Adverse Events

The following will not be considered to be reportable SAEs in this study:

- As all women with type 1 diabetes require hospitalisation for fetal monitoring during delivery, hospitalisation for delivery, including preterm delivery will be exempted
- Hospitalisation for other maternal/fetal indications common to type 1 diabetes pregnancy are recorded as secondary obstetric and neonatal outcomes

The following events occurring after informed consent is provided, and likely to be related to the underlying condition or disease (pregnancy or type 1 diabetes) or likely to represent concomitant illness will be captured in the subject's CRF as expected outcomes and should not be recorded as serious adverse events:

Maternal/Fetal Outcomes:

- Hypertensive disorders of pregnancy (Gestational hypertension, Worsening of pre-existing hypertension, preeclampsia)
- Hyperemesis
- Obstetric reason for admission unrelated to diabetes
- Pregnancy loss: miscarriage or termination before 24 weeks
- Preterm labour or birth
- Severe hypoglycaemia without paramedic call out, emergency department assessment or hospital admission
- Admission for DKA not requiring treatment with VRIII

Infant Outcomes:

- Birth injury
- Congenital or chromosomal anomalies
- High level neonatal care >24 hours
- Neonatal hypoglycaemia
- Hyperbilirubinemia
- Respiratory distress
- Shoulder dystocia

NOTE: Severe hypoglycaemia requiring paramedic assistance, emergency department assessment and/or hospital admission is considered a Serious Adverse Event. Admissions with DKA requiring inpatient treatment with VRIII is considered a Serious Adverse Event. Maternal death, stillbirth and neonatal death are all considered Serious Adverse Events.

Skin reactions:
Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies. These should be reported as adverse events. During each follow-up visit, each location where a study CGM sensor has been worn will be assessed by trial personnel. Both acute and non-acute changes will be documented.

Only where a skin reaction is classified as severe (the observation is extremely noticeable and bothersome or may indicate infection or risk of infection or potentially life- threatening allergic reaction) will a Serious Adverse Event Form be required to be completed.

7.2 Investigator responsibilities relating to safety reporting

Participants will be reviewed for adverse events at all study visits. All non-serious AEs, whether expected or not, should be recorded in the participant's medical notes and on the study database within the timescales detailed in the Data Management Plan. SAEs and SADEs should be notified to NCTU immediately after the investigator / research team become aware of the event (in no circumstance should this notification take longer than 3 calendar days)

7.2.1 Seriousness assessment

When an AE or ADE occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' then an SAE form must be completed and forwarded to NCTU immediately.

7.2.2 Severity or grading of Adverse Events

The severity of all AEs and/or ADEs (serious and non-serious) in this trial should be graded using the following table:

Intensity	Definition
Mild	Participant is aware of signs and symptoms but they are easily tolerated
Moderate	Signs / symptoms cause sufficient discomfort to interfere with usual activities
Severe	Participant is incapable of working or performing usual activities

NB. The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as 'serious', which is based on patient/event outcome or action criteria (see definition in Table 1). For example, itching for several days may be rated as severe, but may not be clinically serious.

7.2.3 Causality

The investigator must assess the causality of all adverse events in relation to the trial intervention using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SADE
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SADE
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SADE

7.2.4 Expectedness

If there is at least a possible involvement of the trial investigational intervention, the Chief Investigator must assess the expectedness of the event. An unanticipated adverse device effect is one that is not

reported in the current risk analysis report, or one that is more frequently reported or more severe than previously reported. If a SADE is assessed as being unanticipated it becomes a USADE (Unanticipated Serious Adverse Device Effect) and REC reporting guidelines apply (see section 7.3: Notifications).

7.3 Notifications

7.3.1 Notifications by the Investigator to NCTU

NCTU must be notified of all SAEs and SADEs **immediately, but not later than 3 calendar days** of the investigator becoming aware of the event. In addition, device deficiencies that **might have** led to a serious adverse event where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are reportable under the serious adverse event reporting system and must be reported **immediately and not later than 3 calendar days** of becoming aware to NCTU.

Investigators should notify NCTU of all reportable safety events occurring from consent until maternal post-partum hospital discharge or the patient's discontinuation in the study. If the participant discontinues with the intervention, SADEs must still be reported until maternal discharge.

The SAE form must be signed off by the Principal Investigator (PI) with attention paid to the severity and causality of the event. In the absence of the PI, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The PI should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the PI to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting person and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the NCTU central safety email account (nctu.safety@uea.ac.uk).

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of Clinical Investigation Plan intervention and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

7.3.2 Device Deficiencies

The site investigator is responsible for promptly notifying NCTU of all device deficiencies via the study database.

Device deficiencies that might have led to a serious adverse event where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are reportable under the serious adverse event reporting system in line with section 7.3.1.

All device deficiencies are reviewed by the CI or delegate to verify the requirements for reporting to the device manufacturer and ethics committee.

7.3.3 Reporting Procedures for SAEs

Medically qualified staff at NCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI (or delegate), both opinions and any justifications will be provided in subsequent reports.

The delegated staff at NCTU will cross reference the SAE against the anticipated device effects in the Investigator Brochure to enable an assessment of expectedness for the purposes of onward reporting. This expectedness assessment will be reviewed and signed off by the CI.

The NCTU will email a copy of the SAE report to the Manufacturer's representative if required in line with contractual requirements to enable their own vigilance reporting requirements.

SAEs should be reported to the main REC within 15 days of the NCTU becoming aware if, in the opinion of the CI, the event was both:

- Related – that is , it resulted from the administration of the device
- Unanticipated – that is, the type of event is not listed in the Investigator Brochure as an expected complication of the device.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial.

Following the CE marking of both previously investigational devices covering the purpose of use in the study, safety events will no longer be reported to the MHRA in real time. NCTU will submit quarterly short safety reports in accordance with the MHRA request.

8 Ethics and Dissemination

8.1 Research Ethics and Health Research Authority Approval

Before initiation of the trial at any clinical site, the Clinical Investigation Plan, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC and to HRA for approval. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the Clinical Investigation Plan, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomization, the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the Clinical Investigation Plan treatment and follow-up without giving a reason and without prejudicing their further treatment.

8.2 Competent Authority Approvals

Originally, the Clinical Investigation Plan was submitted to the MHRA in line with requirements for a Device Study and, as such, a Notice of Non-Objection was obtained from the MHRA prior to commencement of the trial.

The progress of the trial, safety issues and reports, including expedited safety reporting, was reported to the MHRA in accordance with relevant requirements and practices.

Since the CE marking of CamAPS FX and Dexcom G6 for use in pregnancy, the MHRA do not require further amendments to be submitted to them for review, not do they require expedited safety reporting. Going forward, amendments to the Clinical Investigation Plan will be forwarded to the MHRA for notification only.

8.3 Other Approvals

Documentation will need to be submitted to the R&D Department at each NHS Trust in order to gain confirmation of capacity and capability (for English sites) or local R&D approval (for non-English sites) prior to the study being initiated at that Trust.

A copy of the local capacity and capability / R&D approval must be forwarded to the NCTU, before participants are randomised to the trial.

The Clinical Investigation Plan has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

8.4 Amendments

Amendments to the Clinical Investigation Plan and other documents (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the Health Research Authority and Ethics Committee for categorisation and approval. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard HRA processes and timescales. Amendments must not be implemented until HRA approval is received and sites have either confirmed acceptance or, no objection has been received within the defined timescale. Since confirmation of CE mark for both devices, MHRA no longer require notification of subsequent amendments. Notification will be sent by NCTU to trial personnel to confirm when an amendment can be implemented.

8.5 Consent or Assent

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised research team member, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process, it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the NCTU trial team.

8.5.1 Consent or Assent in Ancillary Studies

Permission will be requested from participants to allow the study team to analyse blood samples for future metabolic studies.

8.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. This information will be securely destroyed 10 years after the end of the trial.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs and limiting access to personal information held on the database. At trial enrolment, the patient will be issued a participant identification number and this will be the primary identifier for the patient, with secondary identifiers of date of birth and initials.

The patient's consent form will carry their name and signature. These will be kept at the trial site, with a copy sent to NCTU for monitoring purposes. This copy will be destroyed once checks are complete. Consent forms will not be kept with any additional patient data.

8.7 Declaration of Interests

The investigators named on the Clinical Investigation Plan have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

8.8 Indemnity

The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research. UEA holds insurance to cover harm to participants arising from the design of the study.

8.9 Finance

AiDAPT is fully funded by an NIHR Efficacy and Mechanism grant number 16/35/01. The Jaeb Center for Health Research team input is financially supported by the Juvenile Diabetes Research Foundation.

8.10 Archiving

The investigators agree to archive and/or arrange for secure storage of AiDAPT trial materials and records for 10 years after the close of the trial unless otherwise advised by the NCTU.

8.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG/TSC. Considerations for approving access are documented in the TMG/TSC Terms of Reference.

8.12 Ancillary and Post-trial Care

Devices will be provided to the participants for the duration of the trial. Post-trial care is at the discretion of the woman and her treating clinical team.

8.13 Publication Policy

8.13.1 Trial Results

Data will be published in internationally peer-reviewed scientific journals; members of the investigator group and clinical collaborators will be included as co-authors as appropriate.

The results of the trial will be disseminated regardless of the direction of effect.

8.13.2 Authorship

Authorship will be determined by a publication policy which will be agreed by the TMG.

8.13.3 Reproducible Research

The trial will be registered on the ISRCTN website, granting public access to the trial outcomes. In addition the clinical study protocol will be submitted for publication. Every effort will be made to grant access to the participant-level dataset subject to TSC approval.

9 Outcome Definitions

Booking visit: first antenatal visit following confirmation of pregnancy.

Birth Injury: includes all of the following: spinal cord injury, basal skull fracture or depressed skull fracture, clavicular fracture, long bone fracture (humerus, radius, ulna, femur, tibia or fibula), subdural or intracerebral haemorrhage of any kind [confirmed by cranial ultrasound, computerized tomography (CT) scan, or magnetic resonance imaging (MRI), peripheral nerve injury/brachial plexus.

Neonatal Hyperbilirubinemia: Significant jaundice based on bilirubin levels requiring treatment with either phototherapy > 6 continuous hours, or an exchange transfusion, or receiving intravenous gamma globulin or requiring readmission into hospital during the first 7 days of life due to hyperbilirubinemia.

Neonatal Hypoglycaemia: A capillary glucose <2.6 mmol/L on one or more occasions, within the first 48 hours of life starting at least 30 minutes after birth, and necessitating treatment either with 40% glucose gel administered to the buccal mucosa and/or with intravenous dextrose.

Respiratory distress: Respiratory difficulties requiring any positive pressure ventilation ≥ 24 hours, beyond resuscitation period (10 minutes), and /or given surfactant within 72 hours after birth.

Levels of neonatal care: Level 1 care (also called special care baby unit (SCBU) is for babies who need continuous monitoring of their breathing or heart rate, additional oxygen tube feeding, phototherapy recovery (to treat neonatal jaundice) and convalescence from higher level NICU care. Level 2 care is for babies needing short-term intensive care with apnoeic attacks who require respiratory support, including receiving continuous positive airway pressure (CPAP). Some babies receiving parenteral nutrition or intravenous dextrose may also need this level of care. Level 3 or Neonatal Intensive Care Unit (NICU) is for the most unwell babies, typically those delivered preterm and/or needing respiratory support, or other high level care. Some NHS maternity units also provide transitional care units where the parents are the primary care givers and only minimal staff support is required.

Preterm birth: Preterm birth (<37 weeks and early preterm <34 weeks).

Shoulder Dystocia: Defined as a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed (https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg42/).

Adverse device effect: any untoward and unintended response, any event resulting from insufficiencies in the instructions, use of the device or user error.

Hyperglycaemia: high blood sugar (glucose level).

Hypoglycaemia: low blood sugar (glucose level).

Severe hypoglycaemia: An event requiring assistance of another person actively to administer carbohydrate, glucagon or other resuscitative actions. Severe hypoglycaemia will be categorised as

treated at home with rescue carbohydrates and/or glucagon, requiring ambulance or paramedic call out, requiring hospital admission.

Diabetic ketoacidosis: an episode with elevated plasma ketones which can be categorised as mild/ self-treated (plasma ketones 0.5 – 1.0mmol/mol), moderate/self-treated (plasma ketones > 1.0mmol/mol which resolves without hospital admission), or severe plasma ketones > 1.0mmol/mol and requiring hospital admission and treatment with Variable Rate Intravenous Insulin Infusion (VRIII).

Maternal hypertensive disorders: includes gestational hypertension, worsening of pre-existing hypertension, and/or preeclampsia defined as:

- Gestational hypertension: Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions four hours apart, developing after 20 weeks of gestation in previously normotensive women.
- Pre-eclampsia: Hypertension accompanied by proteinuria ≥300 mg in 24 hours, or two readings of at least ++ on dipstick analysis of urine or documentation of pre-eclampsia in the delivery or antenatal records.
- Preeclampsia superimposed on chronic hypertension: Preeclampsia (as defined above) developing after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

10 Clinical Investigation Plan Amendments

V1.0 to v2.0; 5th December 2018

1. To minimise differences according to increasing intermittent and real-time CGM use amongst control group participants, all participants will be provided with the same CGM system. This allows for the same CGM glucose data to be obtained, reviewed and recorded in both the control and intervention groups.
2. This allows all CGM data from recruitment to delivery to be directly compared in the primary outcome rather than limiting the primary outcome assessment data to 2 x 10 day windows. It also minimizes the difference between the control and intervention arms, increasing equipoise.
3. As there is no need for additional visits for CGM insertion prior to 24 and 34 weeks gestation, the study visit schedule can more closely align with the antenatal scan visits at 28, 32 and 36 weeks.
4. Details of CGM training in the control arm have been added.
5. Timeframe for recruitment visit relaxed to allow recruitment once viable pregnancy has been confirmed via ultrasound. Timeframe for randomisation visit adjusted to allow earlier randomisation in line with earlier recruitment and to allow for training period prior to 15 weeks 6 days.
6. Participant timeline table clarified.
7. Permitted insulin type to be used with the intervention pump expanded to include all short-acting insulins.
8. Clarification added regarding screening logs (section 6.3.1.7)
9. Hospital Anxiety and Depression Scale (HADS) removed from questionnaire pack; Hypoglycaemia Fear Survey Questionnaire II modified to use the worry scale only. Option added to complete questionnaires electronically.
10. Data collection section updated to reflect the role of the Jaeb Center for Health Research. Clarified that data requiring expedited reporting will be sent directly to NCTU.
11. References to Data Protection Act 1998 updated to current data protection legislation.
12. Safety reporting section (7) updated in line with ISO 14155.
13. Trial Committee contact details updated.
14. Section 4 'Glossary' merged with 'Outcome Definitions' (section 9). Definitions clarified.
15. References added / updated.
16. Administrative amendments throughout.

V2.0 to v2.1; 13th March 2019

1. Insulin pump to be used updated to include both Dana Diabecare R and RS versions.
2. Added into closed-loop training that the diabetes educator will check the components of the closed-loop system are working together as expected.
3. Section 7.2.3: Amended to specify that the investigator will assess causality of all AEs (not only SAEs).
4. Administrative correction made to above amendment details – up-versioned from v1.0 to v2.0 (not from 1.0 to 1.1), and date corrected.

V2.1 to v3.0; 29 January 2020

1. Amendment to primary outcome measure in line with a recent international consensus meeting to define Time in Range (TIR) as the proportion of time CGM glucose levels were between 3.5-7.8mmol/L and additional definitions for Time Above Range (TAR) and Time Below Range (TBR). Updates to all outcome statements, abbreviation table and associated reference.
2. Section 7.3, Clarification of timescales and reporting of SAEs and SADEs to the central NCTU safety email account.
3. Page 24, Addition of WHO definition of type 1 diabetes as part of inclusion criteria
4. Pages 26, 27, 32, 34, clarification that training can occur outside of the hospital environment.
5. Page 38, Clarification that sample size refers to the number of randomised participants and not just consented
6. Page 44, Correction of blood sample collection in line with the laboratory manual
7. Page 54, clarification that approach and obtaining consent can be undertaken by an authorised research team member.
8. Section 2.4, update to named research personnel
9. Page 33 and 34, reference to two 'top tips' guidance leaflets to compliment participant training
10. Summary of amendment changes to version 3.0
11. Version number and date updated on title page and filename footer

V3.0 to V4.0; 17th June 2021

1. Dexcom G6 system and CamAPS FX app are now CE marked covering the purpose of use in the study. The MHRA no longer require notification of subsequent amendments or expedited safety reporting.
2. Amendment to contact details for Trial Manager, TSC and DMC members.
3. Allowing GMI estimate of HbA1c levels from Libre or CGM devices (driven by COVID laboratory restrictions and social distancing measures)
4. Including the option of online device training for intervention and control groups and online or telephone research visits (driven by COVID social distancing measures)
5. Added links to generic training modules available to support trial participants and staff
6. Clarification that the intensive insulin therapy eligibility criteria includes women using sensor augmented pumps and/or hybrid closed-loop systems other than CamAPS FX.
7. Clarification that the CE marked insulin pump used may be an upgrade from the original pump specified.
8. Administrative change – 'FlorenceX' updated to 'CamAPS FX' throughout
9. Allowing the CamAPS FX app to be continued for up 8 weeks post-partum, if necessary, to enable safe transition onto post-partum insulin therapy by the usual diabetes clinical care team (an essential mitigation driven by COVID NHS staffing pressures)
10. Clarification that the 'training assessment' should be an exercise to ensure that training has been covered and understood.
11. Clarification of continuous CGM data collection processes
12. Allowing use of study smartphone for participants on the control arm

13. Clarification of withdrawal procedure (to ensure maximum data collection even if participant does not wish to proceed with intervention)
14. Blood samples for future metabolic research are now optional (driven by COVID laboratory restrictions and social distancing measures)
15. Clarification of run-in procedures for participants using a Dexcom G6 sensor prior to enrolment. Removed requirement for masking CGM data as most women will already be using Dexcom G6.
16. Clarification for collection of data for neonatal re-admission for hyperbilirubinemia
17. Clarification of SAE reporting for episodes of DKA requiring hospital admission and treatment with VRIII
18. Updated that post-trial care is at the discretion of the woman and her treating clinical team to allow for increasing available options.
19. Clarification of the booking visit definition
20. Statistical analysis section updated to address optional HbA1c blood samples and include sensitivity analysis for multiple pregnancies.

V4.0 to V5.0; 22nd October 2021

1. Allowing for use of CGM and CamAPS FX to be continued for up to 6 months post-partum (driven by changes to NHS standard care of pregnant women with type 1 diabetes who have access to 12 months of CGM use) – See Appendix 1 for full details, and throughout protocol.
    a. Addition of virtual (telephone or video-call) visits at 8-12 weeks and 24 weeks post-partum, with clarification of the participant timelines and study procedures
    b. Addition of participant feedback descriptive writing at 8-12 and 24 weeks post-partum
    c. Addition of outcomes relating to the post-partum period
2. Clarification that infant outcome 'Hospital length of stay' include re-admissions >24h within the first seven days from birth
3. Addition of exploratory outcomes relating to fetal growth and maternal glucose levels (including collection of data from routine ultrasound scans)
4. Closed-loop training module website link updated
5. Clarification that CGM glucose measures are (usually) uploaded in real-time
6. Allowing for participants to use their own phones with CamAPS FX following CE marking
7. Clarification of the end of study procedures for CamAPS FX app removal
8. Clarification of end of study procedures following early pregnancy loss or miscarriage
9. End of study definition amended and clarified to allow appropriate time for data collection

11 References

1. Maresh MJ, Holmes VA, Patterson CC, Young IS, Pearson DW, Walker JD, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. Diabetes Care. 2015;38(1):34-42.
2. Glinianaia SV, Tennant PW, Bilous RW, Rankin J, Bell R. HbA(1c) and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study. Diabetologia. 2012;55(12):3193-203.
3. Lambert K, Holt RI. The use of insulin analogues in pregnancy. Diabetes, obesity & metabolism. 2013.
4. Kallas-Koeman MM, Kong JM, Klinke JA, Butalia S, Lodha AK, Lim KI, et al. Insulin pump use in pregnancy is associated with lower HbA1c without increasing the rate of severe hypoglycaemia or diabetic ketoacidosis in women with type 1 diabetes. Diabetologia. 2014;57(4):681-9.
5. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347-59.
6. Mello G, Parretti E, Mecacci F, La Torre P, Cioni R, Cianciulli D, et al. What degree of maternal metabolic control in women with type 1 diabetes is associated with normal body size and proportions in full-term infants? Diabetes Care. 2000;23(10):1494-8.
7. Murphy HR, Rayman G, Duffield K, Lewis KS, Kelly S, Johal B, et al. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes Care. 2007;30(11):2785-91.
8. Murphy HR, Elleri D, Allen JM, Harris J, Simmons D, Rayman G, et al. Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. Diabetes Care. 2011;34(2):406-11.
9. Murphy HR, Kumareswaran K, Elleri D, Allen JM, Caldwell K, Biagioni M, et al. Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: a randomized crossover case series. Diabetes Care. 2011;34(12):2527-9.
10. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. N Engl J Med. 2016;375(7):644-54.
11. Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, et al. Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial. Diabetes Care. 2018;41(7):1391-9.
12. Stewart ZA, Yamamoto JM, Wilinska ME, Hartnell S, Farrington C, Hovorka R, et al. Adaptability of Closed Loop During Labor, Delivery, and Postpartum: A Secondary Analysis of Data from Two Randomized Crossover Trials in Type 1 Diabetes Pregnancy. Diabetes Technol Ther. 2018;20(7):501-5.
13. Huyett L, Dassau E, Pinsker JE, Doyle FJ, 3rd, Kerr D. Minority groups and the artificial pancreas: who is (not) in line? Lancet Diabetes Endocrinol. 2016;4(11):880-1.
14. Russell SJ, Beck RW. Design Considerations for Artificial Pancreas Pivotal Studies. Diabetes Care. 2016;39(7):1161-7.
15. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck RW, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593–603.
16. Weissberg-Benchell J, Hood K, Laffel L, Heinemann L, Ball D, Kowalski A, et al. Toward Development of Psychosocial Measures for Automated Insulin Delivery. J Diabetes Sci Technol. 2016;10(3):799-801.
17. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ. 1998;316(7133):736-41.
18. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care. 2005;28(3):626-31.
19. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care. 1987;10(5):617-21.

20. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
21. Feig DS, Asztalos E, Corcoy R, De Leiva A, Donovan L, Hod M, et al. CONCEPTT: Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial: A multi-center, multi-national, randomized controlled trial - Study protocol. BMC Pregnancy Childbirth. 2016;16(1):167.
22. Murphy HR. 2020 NICE guideline update: Good news for pregnant women with type 1 diabetes and past or current gestational diabetes. Diabet Med. 2021 Jun;38(6):e14576. doi: 10.1111/dme.14576.

Appendix 1: Postpartum extension

1 Background and purpose

The implementation of changes, as recommended in the December 2020 NICE guidelines[22], mean that all pregnant women with type 1 diabetes can now access CGM for 12 months. In clinical practice, this means that pregnant women starting CGM at 10-12 weeks gestation and delivering at 36-38 weeks have 5-6 months of NHS funded CGM use after delivery. This disadvantages trial participants who are currently offered 0-8 weeks of CGM use after delivery. This amendment extends the post-partum duration of use of either CGM or closed-loop to 6 months. This brings our study protocol in line with standard NHS care and provides an opportunity to gather important data regarding maternal glucose levels and insulin doses during the first 6 months post-partum.

Participants will be invited to continue with CGM or closed-loop use (as per randomization allocation) following delivery with minimal additional burden for mothers or trial staff and flexible scheduling of virtual study visits at 8-12 and 24 (+/- 2) weeks post-partum.

1.1 Research questions

1) Is the impact of automated insulin delivery compared to a standard regimen of insulin delivery on maternal glycaemic control (including rates of hypoglycaemia) different during the first 6 months postpartum, compared to during pregnancy?
2) What is the psychosocial impact of automated closed-loop insulin delivery on birthing and early maternal experiences of women with type 1 diabetes?

1.1.1 Objectives

1) To describe the longitudinal changes in maternal glycaemia and insulin doses during the first 6 months after delivery of their baby(ies)
2) To understand the psychosocial impact of using automated insulin delivery on participants' experience of birth and the initial days postpartum with their new-born infant(s)
3) To explore whether the treatment effect of automated insulin delivery is different during the first 6 months after delivery compared to during pregnancy

1.1.2 Safety objectives

To determine the impact of automated insulin delivery during the 6-month period post-partum in terms of the frequency, duration and severity of:

1) Severe hypoglycaemia (defined as an event requiring assistance of another person actively to administer carbohydrate, glucagon or other resuscitative actions)
2) Diabetic ketoacidosis
3) Adverse device effect

1.2 Design

This is an exploratory add-on study of AiDAPT participants in the 6 months following delivery, allowing participants the same access to CGM as they would now receive outside of the trial. Standard care for pregnant women with type 1 diabetes now includes 6 months of NHS funded post-partum CGM use. Trial participants will be offered the same duration of CGM use. Participants will continue with either their usual insulin delivery, or closed loop, according to their initial randomization. This follow on has been included to provide an optional, seamless continuation of

gold standard care with minimum burden, and to address key research questions regarding the management of diabetes during the post-partum period.

2 Methods

2.1 Participants

Women participating in the AiDAPT trial willing to continue CGM either with standard insulin pump or injections or with closed-loop insulin delivery (as per their original AiDAPT randomization arm) following delivery through the first 6 months post-partum.

Women who are already taking part in AiDAPT (including those who are in the immediate post-partum phase) may be approached and re-consented to continue their trial participation through the 6-month postpartum period. Participant selection will otherwise be as per main study protocol and participants will be consented to all aspects of the study from initial consent.

2.2 Interventions

2.2.1 Treatment arm:

Treatment arm participants will be offered 6 months post-natal use of the automated insulin delivery system: Dexcom G6 CGM, DANA insulin pump and CamAPS FX. The post-natal glucose target range is 3.9-10.0 mmol/L.

2.2.2 Control arm:

Control arm participants will be offered 6 months post-natal use of the Dexcom G6 CGM alongside their standard insulin delivery (pumps or injections). The post-natal glucose target range is 3.9-10.0 mmol/L.

2.3 Postpartum Outcomes

Key endpoint: Postpartum glycaemic control as assessed by percentage of time spent with CGM glucose levels between 3.9–10.0 mmol/L

2.3.1 Biomedical outcomes:

- Maternal glycaemic control assessed using CGM measures (% time spent above 10.0 mmol/L and below 3.9 mmol/L, frequency & duration of glycaemic excursions, mean glucose & glucose variability
- Maternal insulin regimen (VRIII, insulin pump/injections, closed-loop)

2.3.2 Psychosocial Outcomes:

Self-reported diabetes and treatment-related experience in lived experience as described through free text descriptive writing. Questions to be asked are:

- Thinking about your use of the CGM or closed-loop artificial pancreas, please could you tell us what impact you think it had on the following areas:
    - your feelings about your blood glucose levels, if you used the CGM or closed-loop system: during your child's birth; in the days after giving birth; in the six months after giving birth …
    - thoughts around safety for your health and the health of your baby if you used the CGM or closed-loop: during your child's birth; in the days and weeks after giving birth …

- your relationship with your healthcare team if you used the CGM or closed-loop during your child's birth; and in the initial weeks and months following your child's birth …

2.3.3 Safety outcomes

- The frequency and severity of diabetic ketoacidosis
- The number and severity of episodes of severe hypoglycaemia
- The number and severity of episodes of adverse device effect

2.4 Patient Assessments

2.4.1 Study visits

Study visits will be offered virtually (e.g. using video calls or telephone appointments) to facilitate engagement that suits participants with newborn babies. The following will be collected at around 8-12 and 24 (+/-2) weeks:

- Average total daily dose (TDD) of insulin during the previous 3 days (and insulin type)
- Adverse events
- Details of any issues with devices
- Details of infant feeding (breast, bottle, both, n/a)
- Participant experience feedback (free text descriptive writing) – optional

2.5 Sample size

This is an exploratory add-on to the main study, with the sample size determined by the number of current and future AiDAPT trial participants. At the time of the protocol being amended, 96 of 124 women have been recruited with 60 deliveries and 4 losses to follow up. Most ongoing/future participants are expected to take up the offer of continuing CGM/closed-loop for 6 months after delivery, meaning that by the time the amendment is approved, n=53 is feasible for post-natal evaluation.

2.6 Statistical Methods

2.6.1 Key Postpartum Outcome Analysis

The key analysis will evaluate the change in the time spent in the target glucose range (CGM TIR 3.9 – 10.0 mmol/l) between the intervention and control arm between delivery and 6 months postpartum.

2.6.2 Exploratory Outcome Analyses

- Percentage time spent with CGM <3.0 mmol/l to quantify maternal moderate hypoglycaemia
- Mean CGM glucose
- Percentage time spent with CGM <3.9 mmol/l to quantify borderline hypoglycaemia
- Percentage time spent at CGM >10.0 mmol/l to quantify hyperglycaemia
- Standard deviation (SD) of CGM glucose to quantify the glucose variability
- Coefficient of variation (CV), of CGM glucose to quantify the glucose variability
- Insulin delivered (basal, bolus, and total) to assess insulin needs

- Mild-moderate episodes of hypoglycaemia <3.9 (level 1) and <3.0 (level 2) from CGM data defined as AUC <3.9 or AUC ≤3.0 for 15 minutes duration
- Nocturnal hypoglycaemia (NH): CGM glucose <3.9 (level 1) and <3.0 (level 2) between 23:00 and 07:00 hours

The 24hr (midnight to midnight) and overnight time (23.00-07.00hr) periods will be assessed separately (for percentage TIR 3.9 – 10.0 mmol/L, mean CGM glucose, percentage TAR, percentage TBR, and glucose variability measures (SD,CV).

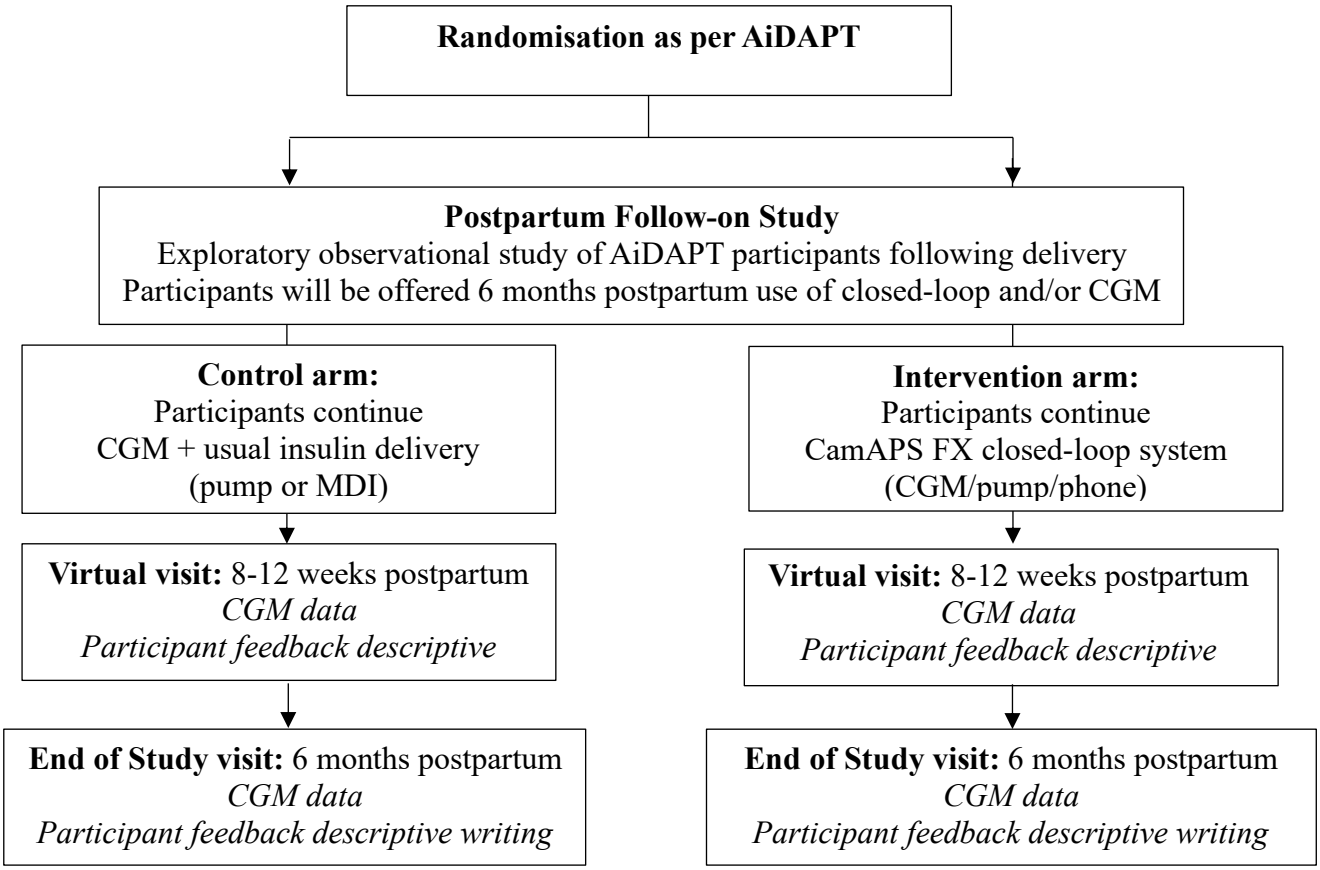
2.6.3 Safety Evaluation

Safety data including number and severity of diabetic ketoacidosis, severe hypoglycaemia and episode of adverse device effects will be tabulated for all participants, including drop-outs and withdrawals, irrespective of whether CGM data are available and irrespective of whether closed-loop was operational. Severe hypoglycaemia events will be defined as events requiring assistance of another person actively to administer carbohydrate, glucagon or other resuscitative actions.

2.6.4 Statistical Analyses

A linear mixed effects regression model will be fit with time in range from trial entry during pregnancy through until 24 weeks post-partum as the dependent variable. The model will adjust for baseline time in range, insulin delivery modality (pump vs MDI) at baseline as fixed effects; and clinical centre and subject as random effects. We will evaluate whether there is a difference in the therapeutic effect of closed-loop between pregnancy and post-partum. Predictive, generalised linear models will be used to explore correlations between maternal insulin doses, infant feeding and postpartum glycaemia.

3 Post-partum follow-on study flowchart



Appendix 2 AiDAPT trial statistical analysis plan

Version History

SAP Version	Author	Approver	Effective Date	Revision Description	Study Stage	Protocol Version
1.0	Peiyao Cheng	Craig Kollman	3/7/19	Original Version	Planning, enrollment not started yet	2.0
2.0	Simon Bergford	Craig Kollman	12/07/22	Added sensitivity analysis for multiple pregnancies. Direct likelihood for handling missing HbA1c values.	Study ongoing	5.0

Approvals

Role	Digital Signature or Handwritten Signature/Date
Author: Simon Bergford	 Dec 8, 202
Senior Statistician: Craig Kollman	 Dec 8, 2022
Jaeb Principal Investigator: Judy Sibayan	 Dec 8, 2022
Study Principal Investigator: Helen R Murphy	 5 Jan 2023
Norwich CTU Trial Statistician: Lee Shepstone	 Jan 11, 2023

Contents

Automated Insulin Delivery among Pregnant Women with Type 1 Diabetes (AiDAPT)

Statistical Analysis Plan

Version 2.0

Corresponds to Version 5.0 of the Protocol

1. Study Overview

1.1. Objectives

The purpose of this study is to determine the biomedical impact of an automated insulin delivery in pregnant women with type 1 diabetes. The detailed study objectives include:

- Efficacy: to assess clinical efficacy of automated insulin delivery in the home setting as compared with standard self-directed insulin delivery in pregnant women with T1D. The primary efficacy objective is to maintain glucose levels within the target range of 3.5-7.8 mmol/l based on subcutaneous CGM measures.
- Safety: to determine the impact of automated insulin delivery in terms of the frequency, duration and severity of severe hypoglycemia, diabetic ketoacidosis, and adverse device effect.
- Human factors: to determine women's perception of automated insulin delivery in terms of diabetes self-management, fear of hypoglycemia, sleep quality, pregnancy experiences and women's work and family lives.
- Health economics: to estimate the additional cost per additional week of target glucose control and to estimate quality adjusted life years.

1.2. Summary of The Study

This is an open-label, multi-center, randomized, two-arm parallel group trial comparing automated closed-loop and standard insulin delivery. The primary outcome is the percentage of time spent with glucose levels between 3.5-7.8 mmol/l based on CGM levels from 16 weeks gestation until delivery. The study will include 124 pregnant women between 18 and 45 years of age with T1D of at least 12 months' duration on standard insulin delivery. These 124 subjects will be randomized into automated insulin delivery (AiD) and standard care (control) two study arms in 1:1 ratio and stratified by study site.

The AiD system to be used in this study will consist of three separate devices: a CE marked subcutaneous insulin infusion pump (Dana Diabecare R), a CE marked real-time CGM system (Dexcom G6), and a CE marked computer-based model predictive control (MPC) algorithm which will compute information from the real-time CGM into a recommended insulin dose (CamAPS FX).

The recruitment visit will happen between ultrasound confirmation of viable pregnancy and 13 weeks and 6 days of gestation. At the recruitment visit, past medical history, weight and height data will be collected among those eligible participants. Baseline questionnaire pack

will be distributed, CGM sensor will be inserted, and the participants will be instructed to wear it at home for up to 10 days.

The randomization visit will happen at up to 15 weeks and 6 days of gestation when CGM sensor will be downloaded, baseline bloods samples will be taken for HbA1c where possible (otherwise GMI may be used), and participants will be randomized to either AiD arm or standard care arm. For the participants randomized to the AiD arm, training on CGM, study pump as well as the automated closed-loop system will be provided post randomization with a maximum of 15 weeks and 6 days gestation. Competency on CGM/pump/closed-loop system use will be evaluated, for those who successfully completed the training, they will proceed to using AiD throughout pregnancy. For the participants randomized to the control arm, training on sensor insertion, CGM data interpretation, dietary advice and insulin dose adjustment will be provided at or following randomization visit with a maximum of 15 weeks and 6 days gestation. After that, participants in the control arm will continue to use current methods of delivering insulin. The study CGM sensors will be inserted, and the control subjects will replace the study CGM sensor every 10 days from recruitment until delivery to provide comparable outcome data with the AiD arm. For both treatment arms, blood samples (for HbA1c measurement) will be collected at 24 and 34 weeks where possible (acknowledging that face-to-face visits and laboratory samples were limited during the covid-19 pandemic), and follow-up questionnaires will be distributed at 34 weeks. Qualitative interviews will be conducted on a subset of women in the AiD arm as soon as possible post-randomization and also at approximately 34 weeks gestation.

Data from the AiDAPT study will be analyzed by two groups. Jaeb Center will be responsible for analyzing the CGM related efficacy outcomes, and the Norwich Clinical Trials Unit (NCTU) team will be responsible for analyzing the maternal obstetric/infant related efficacy outcomes, safety outcomes, psychosocial outcomes, and performing health economics analysis.

1.3. Hypothesis

- Null hypothesis: There is no difference in time spent in the target glucose range 3.5-7.8 mmol/l between those pregnant women who use automated insulin delivery and those who use standard insulin delivery method during the second and third trimester.
- Alternative hypothesis: There is a nonzero difference (two-sided) in time spent in the target glucose range 3.5-7.8 mmol/l between those pregnant women who use automated insulin delivery and those who use standard insulin delivery method during the second and third trimester.

1.4. Sample Size

The power calculations aim to compare the effect of closed-loop on the time spent in the target glucose range 3.5-7.8 mmol/l and are based on data from our previous studies of CGM and closed-loop in pregnancy. To detect a 10% absolute difference the time spent in the CGM target glucose range between automated closed loop and standard insulin delivery, assuming

SD of 15%, 98 participants are needed to achieve 90% power and an alpha level of 0.05 (two-tailed). Adjusting for approximately 10% pregnancy loss and 10% of randomized participants who withdraw, the sample size will be 124 total (62 per arm).

2. Outcome Metrics

2.1. Primary Efficacy Endpoint:

- CGM % time in range 3.5-7.8 mmol/l based on CGM levels between 16 weeks gestation and delivery (63-140 mg/dL)
-

2.2. Secondary Efficacy Endpoints

2.2.1. Key Secondary Glycemic Endpoints

- Overnight (23:00-07:00) percentage time in target range (63-140 mg/dL)
- Percentage time above target (>7.8 mmol/l) (>140 mg/dL)

2.2.2. Other Maternal Secondary Glycemic Endpoints

- International consensus targets TIR 3.5-7.8mmol/L >70% (16hr 48 min), TAR >7.8mmol/L <25% (6hr), TBR <3.5mmol/L <4% (1hr), and TBR <3.0mmol/L <1% (15min) (63-140, >140, <63, & <54 mg/dL)
- Percentage time spent with CGM 3.5-10.0 mmol/l (63-180 mg/dL)
- Mean CGM glucose
- CGM glucose standard deviation (SD)
- CGM glucose coefficient of variation (CV)
- Percentage time spent with CGM <3.5 mmol/l (<63 mg/dL)
- Percentage time spent with CGM <3.0 mmol/l (<54 mg/dL)
- AUC of glucose <3.5 mmol/l (<63 mg/dL)
- AUC of glucose <3.0 mmol/l (<54 mg/dL)
- Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI)
- Percentage time spent with CGM > 10.0 mmol/l (>180 mg/dL)
- AUC of glucose >7.8 mmol/l (>140 mg/dL)
- AUC of glucose >6.7 mmol/l (>120 mg/dL)
- Mild-moderate episodes of hypoglycaemia <3.5 (level 1) and <3.0 (level 2) from CGM data defined as AUC<3.5 or AUC ≤3.0 for 15 minutes duration (<63 & <54 mg/dL). Episodes end once CGM glucose is ≥3.5 or ≥3.0. Distinct episodes must be separated for at least 30 minutes.
- Nocturnal hypoglycaemia (NH): episodes of CGM glucose <3.5 (level 1) and <3.0(level 2) between 23:00 and 07:00 hours for 15 minutes duration (<63 & <54 mg/dL). Episodes end once CGM glucose is ≥3.5 or ≥3.0. Distinct episodes must be separated for at least 30 minutes.
- HbA1c

2.2.3. Insulin Endpoints

- Total daily insulin
- Daily basal insulin
- Daily bolus insulin

2.2.4. Maternal Obstetric Outcomes

- Gestational weight gain (weight gain from baseline to 36 weeks)
- Gestational hypertension or preeclampsia
- The Mode of delivery (vaginal, instrumental, elective caesarean section and emergency caesarean section)
- The gestational age at delivery and indication for any preterm delivery (<37 weeks)
- Adverse events including pregnancy loss <24 weeks, stillbirth, neonatal death
- Maternal hospital admissions
- Hospital length of stay

2.2.5. Infant Outcomes

- Neonatal morbidity including treatment for neonatal hypoglycaemia, neonatal jaundice and respiratory distress between the time of infant delivery and discharge from hospital.
- Infant birth weight (customised birth weight percentile, incidence of large for gestational age (LGA), and small for gestational age (SGA)
- Neonatal intensive care unit (NICU) admission >24 hours
- Infant feeding at hospital discharge: breast, bottle, both
- Hospital length of stay (from delivery until hospital discharge) including readmissions >24h within the first seven days from birth

2.2.6. Safety Outcomes

- The frequency and severity of diabetic ketoacidosis during the period of inclusion in the trial
- The number and severity of episodes of severe hypoglycaemia during the period of inclusion in the trial
- The number and severity of episodes of adverse device effect

2.2.7. Questionnaires

Data from the following questionnaires will be summarized at baseline and 34-36 weeks. The between group difference of each score at 34-36 weeks will be assessed:

- The INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE) questionnaire (intervention group only)
    - Mean score of all items multiplied by 25 with higher scores indicating more positive appraisal of automated insulin delivery
- The EQ-5D Health-Related Quality of Life Questionnaire
    - Sum of all items scored 1-5 with higher scores indicating worse health states
- The Diabetes Distress Scale (DDS)
    - Total score – average of all responses with higher scores indicating more distress
    - Emotional burden – average of items 2, 4, 7, 10, and 14
    - Physician Distress – average of items 1, 5, 11, and 15
    - Regimen Distress – average of items 6, 8, 3, 12, and 16
    - Interpersonal Distress – average of items 9, 13, and 17
- The Hypoglycaemia Fear Survey Questionnaire II (HFSQ II) (Worry scale only)
    - Sum of all 17 items with higher scores indicating increased fear of hypoglycemia
- Pittsburgh Sleep Quality Index (PSQI)
    - Total score – sum of each component score with higher scores indicating worse sleep quality
    - Subjective sleep quality – question 9
    - Sleep latency – questions 2 (≤15 minutes = 0, 16-30 = 1, 31-60 = 2, >60 = 3) and 5a, sum of Q2 and Q5a – 0 = 0, 1 or 2 = 1, 3 or 4 = 2, 5 or 6 = 3
    - Sleep duration – question 4 (>7 hours = 0, 6-7 = 1, 5-6 = 2, <5 = 3)
    - Sleep efficiency – questions 1, 3, and 4, sleep efficiency = (# hours slept/#hours in bed)*100%, #hours in bed – calculated from q1 and q3 - >85% = 0, 75-84% = 1, 65-74% = 2, <65% = 3
    - Sleep disturbance – sum of questions 5b-5j – 0 = 0, 1-9= 1, 10-18 = 2, 19-27 = 3
    - Use of sleep medication – question 6
    - Daytime dysfunction – sum of questions 7 and 8 – 0 = 0, 1 or 2 = 1, 3 or 4 = 2, 5 or 6= 3

The INSPIRE questionnaire assesses psychosocial aspects of technology including expectations, psychosocial functioning, impact on self-management, impact on health, usability, wearability and burden. Items are scored on a 5-point scale from ‘strongly agree’ through ‘strongly disagree’. Specific questions are asked to address regulatory approvals and concerns around managing AiD expectations. It is applicable only to the intervention group.

The EQ-5D Health-Related Quality of Life Questionnaire is a self-rated health status using a visual analogue scale. It provides a self-reported description of current health in 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The concept of health in EQ-5D also encompasses both positive aspects (well-being) and negative aspects (illness). The utility score is an expression of the Quality Adjusted Life Years (QALY).

The Diabetes Distress Scale (DDS) assesses worries and concerns specifically related to diabetes and its management; it has been shown to be a good marker of factors important to diabetes-related quality of life and has good reliability (alpha ≥0.87) and validity. The newer DDS for T1D includes 17 items. Responses are rated on a 6-point scale from 'not a problem' to 'a very serious problem'. Four sub-domains, in addition to a total score, provide detailed assessments of emotional burden, physician-related distress, regimen-related distress, and diabetes-related interpersonal distress.

The Hypoglycaemia Fear Survey Questionnaire is a validated questionnaire to measure several dimensions of fear of hypoglycaemia. The modified questionnaire to be used within this trial consists of a 13-item "Worry subscale" that measures anxiety and fear surrounding hypoglycaemia.

The PSQI is a validated 19-item questionnaire that holistically assesses sleep quality and sleep duration over the preceding month.

2.2.8. Health Economic Outcomes

The cost-effectiveness of the closed loop system will be estimated using the study primary outcome measure of time spent with glucose levels between 3.5-7.8 mmol/L. This cost-effectiveness study will estimate any additional cost per additional week of in-target glucose control. Additionally, collection of the EQ-5D-5L will enable estimation of quality adjusted life years (QALYs) for a cost-utility analysis.

- Cost of the AiD closed-loop system (cost of the study pump, CGM, and control algorithm). Details of the purchase price and of the use of sensor and pump consumables based on typical or expected usage, will be estimated.
- Cost of the control-arm glucose monitoring and insulin delivery
- Training costs for AiD and control arms
- Maternity health care use for AiD and control arm:
    - NHS antenatal clinic visits
    - Between visit contacts which will be logged and grouped as a) Questions around diabetes management, b) Technical Issues with the devices, c) Questions relating to both 1 and 2 above
    - Antenatal hospital admissions (number and total length of hospital stay) including the delivery admission length of hospital stay
- Neonatal health care use for AiD and control arms:

    - Costs of delivery vaginally or by caesarean section
    - Costs associated with any complication of delivery, and neonatal complications
    - Neonatal intensive care unit admissions (level of care and duration of admission)
    - Total neonatal length of hospital stay
- The EQ-5D Health-Related Quality of Life Questionnaire

2.3. Calculation of CGM Outcomes

Indices will be calculated at baseline and during follow-up is described below.

2.3.1. Baseline

CGM variables will be calculated based on data obtained in the run-in period prior to randomization. Each recruited subject will wear a study CGM sensor at home during run-in for up to 10 days, then return for CGM sensor data uploading within 14 days. At least 96 hours of CGM glucose values with 24 hours of glucose values during 11pm-7am will be required for randomization, if there are difficulties and/or inadequate CGM data, a second CGM sensor will be provided. In these cases, to avoid large gaps in the data, we will include CGM data in 14 days prior to randomization date, and if less than 96 hours of data obtained, will go back 1 day at a time until reach 96 hours or 28 days prior to randomization whichever comes first.

2.3.2. Follow-up

For both AiD arm and control arm, CGM data from the 16 weeks gestation until delivery will be used to calculate all CGM metrics above for the intervention phase. If a subject miscarries or has terminated pregnancy, CGM data until that day will be included for calculating CGM metrics. Minimum 96 hours of CGM data are required for the calculation.

CGM metrics will also be calculated for the following subsets of time with minimum 24 hours data required in each time period:

- First trimester (from the day after randomization until 12 weeks 6 days gestation)
- Second trimester (13-27 weeks 6 days gestation)
- Third trimester (28 weeks until delivery)
- Overnight (23:00-07:00 from 16 weeks' gestation until delivery)

2.4. HbA1c and Insulin Outcomes

HbA1c data and insulin data will be collected in CRFs. Baseline data will be collected at the recruitment visit, and the earliest HbA1c measured during pregnancy will be used. . The analysis windows for 24 weeks and 34 weeks outcomes are stated in below table. If no value is available for HbA1c, GMI will be substituted. GMI will be calculated using CGM data from gestation weeks 23 to <26 and weeks 33 to <36. If no value is available for insulin within the analysis window, the corresponding outcome will be treated as missing.

Visit	Analysis Window
Recruitment	Between first day of LMP and 13+6 weeks gestation
24 weeks	20 to <30 weeks gestation
34 weeks	30 weeks to delivery

Insulin dose (basal, bolus, and total) changes between delivery and 6 months postpartum.

3. Analysis Datasets and Sensitivity Analyses

3.1. Analysis Datasets

The primary and secondary analyses will follow intention-to-treatment approach, which means subjects will be analyzed in the treatment arm assigned by randomization regardless of compliance. All randomized subjects will be included in the primary analysis. For the secondary analyses, only subjects with non-missing outcome data will be included.

3.2. Sensitivity Analyses

3.2.1. Per Protocol Analysis

A per-protocol analysis of the primary endpoint will be performed including subjects who meet the following criteria

- Participants who complete or deliver prior to the 34-36 weeks visit
- Minimum of 96 hours CGM data from 16-week gestation until delivery
- Intervention arm: closed-loop active for at least 60% of the time.

If fewer than 10% of randomized subjects would be excluded based on these criteria, then the per-protocol analysis will not be performed.

3.2.2. Sensitivity Analysis for Multiple Pregnancies

A sensitivity analysis for the primary outcome will be performed to assess impact of including only a participant's first pregnancy in the analysis. The model for the sensitivity analysis will be the same as the model for the primary analysis, except there will be no random subject term.

3.2.3. Confounding

A sensitivity analysis will also be conducted for the primary endpoint if potential confounding factors collected at baseline are detected. The baseline factors listed in Section 11 will be assessed for imbalance between treatment groups.

The imbalance will be assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value. All variables obtained on a continuous scale will be entered into the models as continuous variables unless it is determined that a variable does not

have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored.

3.2.4. Missing Data

Missing data will be handled using multiple imputation with pattern mixture models (Section 6) for the primary analysis. It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used.

To that end, sensitivity analyses will be performed to check whether results are meaningfully different when using alternate methods for handling missing data. The primary analysis will be replicated using:

- Direct likelihood method (MMRM model)
- Rubin's multiple imputation with treatment group in the imputation model

4. Analysis of Primary Outcome

The primary outcome in this study is the percentage of time spent with glucose levels between 3.5-7.8 mmol/l based on CGM levels from 16 weeks gestation until delivery.

Mean ± SD will be tabulated by treatment group at baseline and intervention phase (16 weeks gestation to delivery). A linear mixed effects regression model will be fit with time in range from 16 weeks gestation until delivery as the dependent variable adjusting for baseline time in range, insulin delivery modality (pump vs MDI) at baseline and clinical center and subject as random effects. Subject effects will account for correlated data if some participants are enrolled for multiple pregnancies. If no participants have multiple pregnancies, then the model will not have a subject effect. A point estimate, 95% confidence interval and two-sided p-value will be reported for the treatment effect based on the linear regression model and a 5% level will be used to declare statistical significance. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then a transformation or robust statistical methods will be used instead. However, previous experience suggests that % time glucose in target range will follow an approximately normal distribution.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in the sensitivity analyses by including factors potentially associated with the outcome for which there is an imbalance between groups (Section 5).

4.1.1. Missing Data

In the primary analysis, missing data will be handled using multiple imputation with pattern mixture models assuming the dropout trajectory of the treatment subjects was that of the control arm. All randomized subjects will be included in the imputation.

5. Analysis of Secondary Outcomes

For HbA1c, CGM and insulin endpoints, mean ± SD or percentiles appropriate for the distribution of each endpoint will be tabulated by treatment group at baseline and intervention phase. Similar mixed-effects linear regression models as describe above for primary outcome will be used to calculate p-values for all secondary outcomes. For outcomes with skewed distribution (such as metrics in hypoglycemic ranges, episodes of hypoglycemia calculated as event rates per week), a transformation (i.e. ranked normal transformation) or robust statistical methods will be used instead. For the CGM targets, a mixed effects logistic regression model will be fit adjusting for baseline value, insulin delivery modality at baseline, and clinical center and subject as random effects. Subject effects will account for correlated data if some participants are enrolled for multiple pregnancies. If no participants have multiple pregnancies, then the model will not have a subject effect.

Since HbA1c measurements were limited during the covid-19 pandemic, there may be a large number of missing values. HbA1c values will not be imputed. Direct likelihood will be used to handle missing HbA1c values.

For following selected CGM metrics, p-values will also be calculated separately for overnight period and by trimester:

- Percentage time in target range 3.5-7.8 mmol/l (key secondary endpoint)
- Mean CGM glucose
- Percentage time >7.8 mmol/l
- Percentage time <3.5 mmol/l
- CGM glucose standard deviation (SD)
- CGM glucose coefficient of variation (CV)

For the maternal obstetric and Infant outcomes, summary statistics appropriate to the distribution will be given for continuous data and for binary and other categorical data, the number and percentage will be reported for each category. The analysis of these outcomes will be analogous to the approach outlined above. Linear mixed models will be used for variables with normally distributions, or continuous variables transformed to normal. Logistic binomial regression models will be used, with repeated measures for multiple pregnancies, for binary outcomes or multinomial regression for categorical outcomes (e.g. mode of delivery, infant feeding at discharge). A Poisson model will be used to model maternal hospital admissions.

6. Subgroup Analyses

The treatment effect in subgroups based on baseline factors will be assessed in pre-planned subgroup analyses. These analyses will be conducted to determine whether a similar trend to the overall treatment effect is seen in these subgroups. The study is not expected to have

sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment effect. In the absence of any significant treatment effects in the primary analysis, assessment of subgroups will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

The planned subgroups analysis for the primary endpoint are as follows:

- Insulin delivery modality (pump vs MDI)
- Baseline HbA1c (<7.5% vs ≥7.5%)
- Maternal age
- Clinical site

For each subgroup, the change in percentage of time spent with glucose levels between 3.5-7.8 mmol/l from baseline to intervention phase will be tabulated by treatment group. Interactions between the subgroup factor and the treatment group and visit will be tested in the longitudinal linear regression models as described for primary outcome.

A test for random treatment by center interaction effects will be performed. If significant then a forest plot of the estimated random treatment effect and its 99% CI for each site will be evaluated. Participants missing any baseline values will be excluded from the corresponding subgroup analysis. HbA1c values will not be imputed.

7. Multiple Comparisons

7.1. Primary Endpoint

For the primary endpoint, a single p-value will be reported, thus no multiplicity issue exists.

7.2. Secondary Endpoints

The comparison of secondary endpoints are considered exploratory, the false discovery rate (FDR) will be calculated using the Benjamini-Hochberg method (Benjamini, 2001) adapted using the two-stage test (TST; Benjamini, 2006). FDR adjusted p-values will be calculated separately for the following categories:

- HbA1c outcome and CGM outcomes in 24h overall analyses
- CGM outcomes in overnight analyses
- CGM outcomes in separate trimester analyses
- Insulin outcomes
- Subgroup analyses
- Questionnaires

P-values from sensitivity or safety analyses will not be adjusted for multiple comparisons.

8. Protocol Adherence and Retention

The following tabulations and analyses will be performed according to treatment group:

- A flow chart accounting for all subjects according to treatment group for all visits
- Visit completion rates for each follow-up visit according to treatment group
- Protocol deviations
- Number of and reasons for unscheduled visits and phone calls

9. Baseline Descriptive Statistics

The following baseline demographic and clinical characteristics by treatment group will be summarized in a table. For continuous variables, summary statistics appropriate to the distribution will be given. For discrete variables, number and percentage will be reported for each category. No p-values will be reported for baseline characteristics.

- Age
- Race/ethnicity
- Education
- Diabetes duration
- BMI at recruitment
- Maternal weight at recruitment
- Method of glucose monitoring at recruitment
- Method of insulin delivery at recruitment
- Gestational age at recruitment
- Gestational age at randomization
- HbA1c at recruitment
- HbA1c at randomization
- Diabetes complications (recorded as any of retinopathy, nephropathy, neuropathy as well as individually)
- Chronic hypertension
- Earliest Systolic BP
- Earliest Diastolic BP
- SH in the last 12 months
- DKA in the last 12 months
- Smoking status
- Alcohol use status
- CGM use

10.Planned Interim Analyses

No formal interim analysis is planned for this study.

11.Additional Tabulations and Analyses

11.1. CGM Sensor Use and Closed Loop System Use Assessment

The amount of CGM use in the AiD arm will be calculated over the period starting from the day after treatment started until the delivery date or miscarriage date (if this happens) whichever is earlier. If a subject drops out of the study earlier, then they will be counted as zero use from that point forward until the actual delivery date (if it is known) or the predicted delivery date (if the actual delivery date is unknown). If a subject has miscarriage or preterm birth, that subject will not be included in the denominator after the miscarriage/preterm birth date when calculating percentage of CGM use. The amount of closed loop system use in the AiD arm will be calculated in a similar manner.

Boxplots will be created for % time closed loop system use and % time CGM use overall, by day and night, and by 4-weekly period in the AiD treatment arm.

For the control group, the amount of CGM data in the post-randomization period throughout pregnancy will be summarized similarly for those participants to the AiD group.

11.2. Device Issues

The frequency for different types of device issues will be summarized for both treatment groups. Listing of all device effects will be reported by study site and treatment group.

12.Exploratory Analyses

12.1. System Use vs Glycemic Outcome

Scatterplots will be created for system use in the AiD arm vs HbA1c at 34 weeks and selected CGM metrics in the intervention phase. Spearman correlation between system use and each selected outcome will be reported.

12.2. Maternal Obstetric Outcomes

Summary statistics appropriate to the distribution will be reported for fetal growth outcomes: ultrasound estimated fetal weight, head and abdominal circumference measurements.

12.3. Infant Outcomes

Infant feeding at 8-12 weeks postpartum and 6 months postpartum will be summarized. The number and percentage will be reported for each category.

12.4. Post-Partum Analysis

The key post-partum analysis will evaluate the time spent in the target glucose range (CGM TIR 3.9 – 10.0 mmol/l) between delivery and 6 months postpartum.

- Other exploratory outcomes include: CGM metrics (time above and below target range, Hypoglycaemia events, Low Blood Glucose Index (LBGI), glucose variability measures (CV, SD), mean CGM glucose.

13.References

Benjamini YB, Yekutieli D: The control of the false discovery rate in multiple testing under dependency. *Ann Stat*, 2001; 29(4):1165-1188.

Benjamini YB, Krieger AM, Yekutieli D: Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*, 2006; 93(3):491-507.

Mallinckrodt CH, Clark WS, et al: Assessing responses profiles from incomplete longitudinal clinical trial data under regulatory considerations, *J. Biopharm. Stat.*, 2003; 13(2): 179-190.

Appendix 3 Questionnaires

Euroqol Five Dimensions Health-Related Quality of Life Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

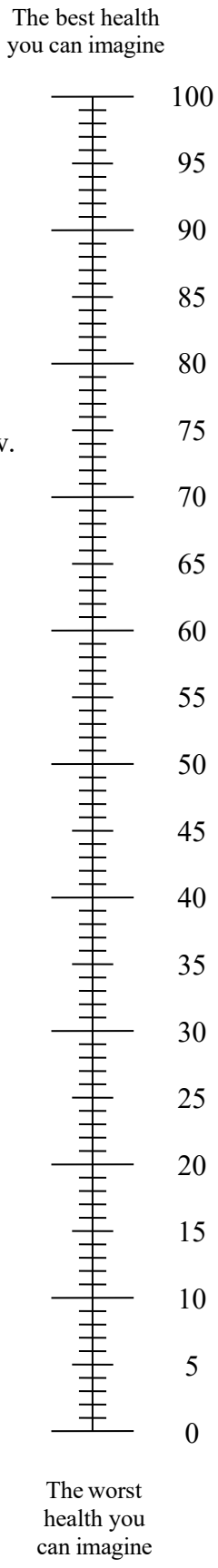
I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY ☐



Diabetes Distress Scale

DIRECTIONS: Living with diabetes can sometimes be tough. There may be many problems and hassles concerning diabetes and they can vary greatly in severity. Problems may range from minor hassles to major life difficulties. Listed below are 2 potential problem areas that people with diabetes may experience. Consider the degree to which each of the 2 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

Please note that we are asking you to indicate the degree to which each item may be bothering you in your life, NOT whether the item is merely true for you. If you feel that a particular item is not a bother or a problem for you, you would circle "1". If it is very bothersome to you, you might circle "6".

	Not a Problem	**A Slight Problem**	**A Moderate Problem**	**Somewhat Serious Problem**	**A Serious Problem**	**A Very Serious Problem**
1. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
2. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6

DIRECTIONS: Living with diabetes can sometimes be tough. There may be many problems and hassles concerning diabetes and they can vary greatly in severity. Problems may range from minor hassles to major life difficulties. Listed below are 17 potential problem areas that people with diabetes may experience. Consider the degree to which each of the 17 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

Please note that we are asking you to indicate the degree to which each item may be bothering you in your life, NOT whether the item is merely true for you. If you feel that a particular item is not a bother or a problem for you, you would circle "1". If it is very bothersome to you, you might circle "6".

	Not a Problem	**A Slight Problem**	**A Moderate Problem**	**Somewhat Serious Problem**	**A Serious Problem**	**A Very Serious Problem**
1. Feeling that diabetes is taking up too much of my mental and physical energy every day.	1	2	3	4	5	6
2. Feeling that my doctor doesn't know enough about diabetes and diabetes care.	1	2	3	4	5	6
3. Feeling angry, scared, and/or depressed when I think about living with diabetes.	1	2	3	4	5	6
4. Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	1	2	3	4	5	6
5. Feeling that I am not testing my blood sugars frequently enough.	1	2	3	4	5	6
6. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6
7. Feeling that friends or family are not supportive enough of self-care efforts (e.g. planning activities that conflict with my schedule, encouraging me to eat the "wrong" foods).	1	2	3	4	5	6
8. Feeling that diabetes controls my life.	1	2	3	4	5	6

	Not a Problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
9. Feeling that my doctor doesn't take my concerns seriously enough.	1	2	3	4	5	6
10. Not feeling confident in my day-to-day ability to manage diabetes.	1	2	3	4	5	6
11. Feeling that I will end up with serious long-term complications, no matter what I do.	1	2	3	4	5	6
12. Feeling that I am not sticking closely enough to a good meal plan.	1	2	3	4	5	6
13. Feeling that friends or family don't appreciate how difficult living with diabetes can be.	1	2	3	4	5	6
14. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
15. Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	1	2	3	4	5	6
16. Not feeling motivated to keep up my diabetes self management.	1	2	3	4	5	6
17. Feeling that friends or family don't give me the emotional support that I would like.	1	2	3	4	5	6

Hypoglycaemia Fear Survey II (worry scale only)

Hypoglycaemic Fear Survey

This survey is intended to find out more about how low blood sugar makes people feel. Please answer the following questions as frankly as possible.

Worry. Below is a list of concerns people with diabetes sometimes have. Please read carefully. Circle one of the numbers to the right that best describes how often you worry about each item because of low blood sugars.

	Never	Rarely	Sometimes	Often	Very often
Not recognising/realising I am having a reaction	1	2	3	4	5
Not having food, fruit, or juice with me	1	2	3	4	5
Feeling dizzy or passing out in public	1	2	3	4	5
Having a reaction while asleep	1	2	3	4	5
Embarrassing myself or my friends in a social situation	1	2	3	4	5
Having a reaction while alone	1	2	3	4	5
Appearing stupid or drunk	1	2	3	4	5
Losing control	1	2	3	4	5
No one being around to help me during a reaction	1	2	3	4	5
Having a reaction while driving	1	2	3	4	5
Getting a bad evaluation at work because of Something that happens when my sugar is low	1	2	3	4	5
Having seizures or convulsions	1	2	3	4	5
Difficulty thinking clearly when responsible for others (children, elderly, etc)	1	2	3	4	5
Developing long term complications from frequent low blood sugar	1	2	3	4	5
Feeling light-headed or faint	1	2	3	4	5
Having an insulin reaction	1	2	3	4	5

Pittsburgh Sleep Quality Index (PSQI)

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

g) Feel too hot

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

i) Have pain

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

INsulin delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE)

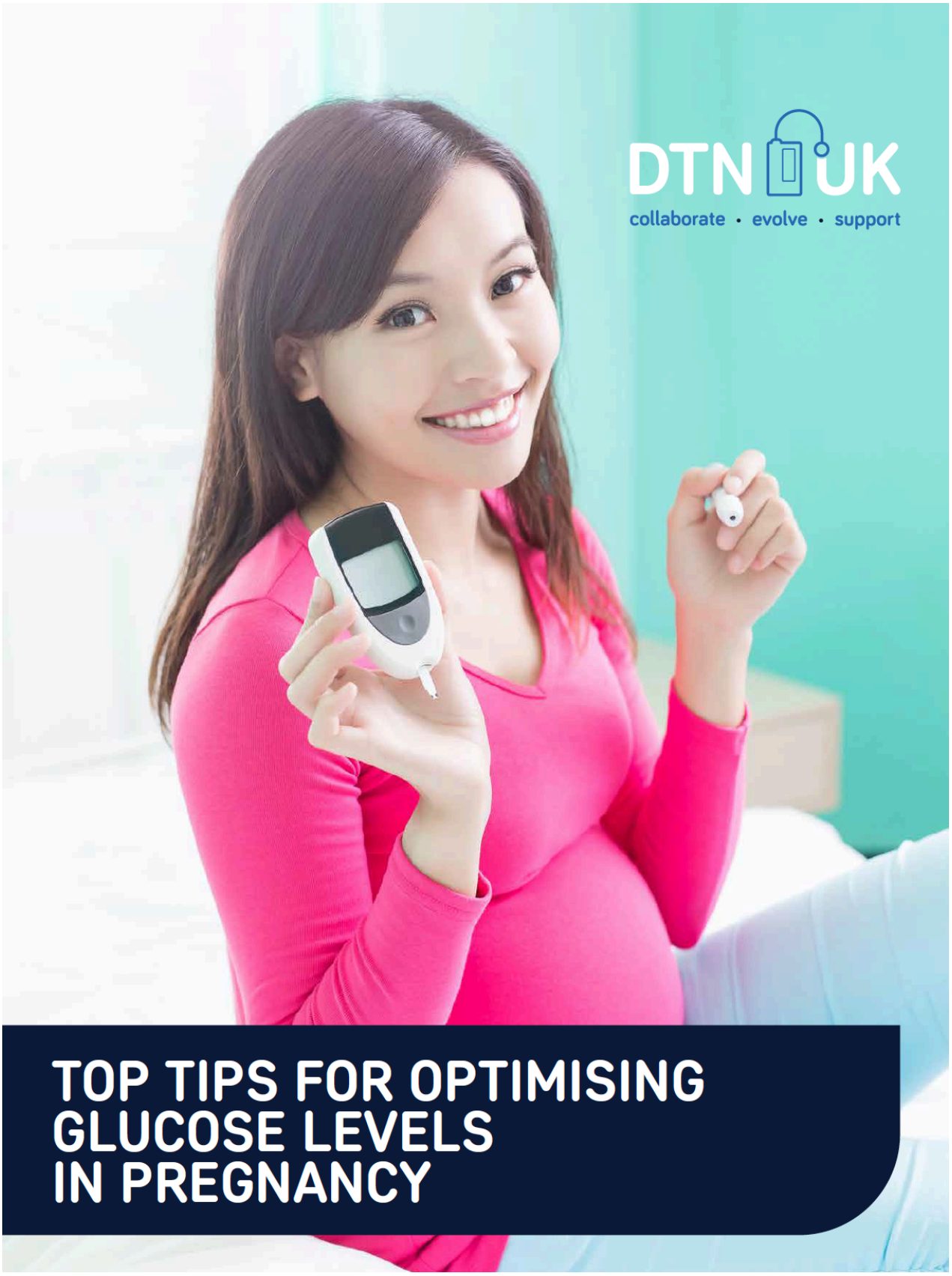
We would like to ask about your thoughts and feelings about your experience using an automated insulin delivery system (**abbreviated AID**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may have been better or worse by using **AID**. **For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I was more hopeful about my future when using an automated insulin delivery (AID).	☐	☐	☐	☐	☐	☐
2	I worried less about diabetes with AID.	☐	☐	☐	☐	☐	☐
3	AID reduced my family's concerns about my diabetes.	☐	☐	☐	☐	☐	☐
4	AID made it easier for me do the things that I wanted to do without diabetes getting in the way.	☐	☐	☐	☐	☐	☐
5	AID decreased how often I had low glucose levels.	☐	☐	☐	☐	☐	☐
6	AID decreased how often I had high glucose levels.	☐	☐	☐	☐	☐	☐
7	AID helped me stay in my target range more often.	☐	☐	☐	☐	☐	☐
8	AID improved my A1c to target level.	☐	☐	☐	☐	☐	☐
9	AID made it easier to eat when I wanted to.	☐	☐	☐	☐	☐	☐
10	AID made it easier to exercise when I wanted to.	☐	☐	☐	☐	☐	☐
		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
11	AID made managing diabetes easier when I was at work or school.	☐	☐	☐	☐	☐	☐
12	AID made managing diabetes easier when driving (for those who drive) or when traveling.	☐	☐	☐	☐	☐	☐
13	AID made managing diabetes easier when it came to my social life/being with friends.	☐	☐	☐	☐	☐	☐
14	AID helped me manage diabetes when it came to my sex life.	☐	☐	☐	☐	☐	☐
15	AID helped me manage diabetes when I chose to drink alcohol.	☐	☐	☐	☐	☐	☐

16	AID helped me manage sick days.	☐	☐	☐	☐	☐	☐
17	AID reduced my risk of long term complications.	☐	☐	☐	☐	☐	☐
		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
18	AID helped me sleep better.	☐	☐	☐	☐	☐	☐
19	I had fewer lows during the night with AID.	☐	☐	☐	☐	☐	☐
20	AID improved my overall quality of life.	☐	☐	☐	☐	☐	☐
21	AID improved my family's overall quality of life.	☐	☐	☐	☐	☐	☐

Appendix 4 Training Resources for Trial Staff and Participants

DTN UK | Top tips for optimising glucose levels in pregnancy



WELCOME

- Working to achieve the best possible glucose levels for pregnancy can feel challenging at times.
- There are certain actions that make a big difference to glucose levels and they are listed below.
- Tick off the ones you feel you are getting right so you can identify the next action to focus on.

EATING THE RIGHT TYPE OF CARBOHYDRATE

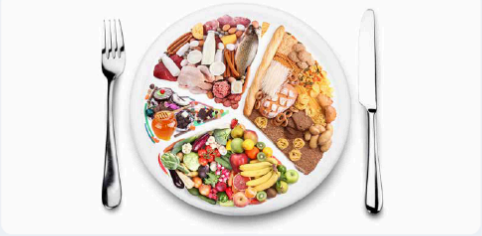
Different carbohydrates can have very different effects on blood glucose levels after eating. Choosing the right type of carbohydrate can make all the difference to keeping the 1 hour post meal glucose below the target of 7.8mmols/l.

Carbohydrates that are unrefined, high in fibre with a low glycaemic index (below 55) create a slower and lower rise in glucose levels after eating.

The table attached lists the foods that most women find don't work well in pregnancy with better alternatives.

ACTION DONE (TICK BOX): ☐

EATING THE RIGHT AMOUNT OF CARBOHYDRATE



It is important to eat enough carbohydrate to provide enough energy and nutrition to support a healthy pregnancy.

However too much carbohydrate makes it impossible to achieve the post meal glucose targets.

Carbohydrate is better tolerated when eaten in smaller quantities so eating small amounts at meals with carbohydrate containing snacks between can be very helpful.

You may find the carbohydrate amounts below a good place to start.

- **Breakfast:** 15-20g carbohydrate
- **Lunch and dinner:** 40-60g carbohydrate
- **Mid-meal snacks:** 10-15g carbohydrate

ACTION DONE (TICK BOX): ☐

TIMING OF BOLUS INSULIN

Giving your bolus insulin ahead of eating can help limit the post meal rise in glucose levels

In early pregnancy giving insulin 10-15 minutes before and as your pregnancy progresses extending this time to 30-40 plus minutes.

ACTION DONE (TICK BOX): ☐

GETTING BREAKFAST RIGHT

Breakfast is the most challenging meal for keeping the post meal glucose in target; carbohydrate is not well tolerated at this time of day. Most women have to spread their breakfast over 2 smaller meals containing 15-20g.

Good breakfast choices:

- 1 slice whole-wheat toast (C15g) with a topping e.g. poached or scrambled eggs / mushrooms / tomato / cheese / ham / bacon / avocado.
- 1 small pot yoghurt (C13g) with one small chopped fruit or cup of berries (C7g) topped with nuts / seeds
- 25g jumbo porridge oats (C15g) soaked overnight in crème fraiche and 1 cup berries (C7g), top with nuts / seeds
- 40g jumbo porridge oats (C25g) cooked with water and single cream added to taste

ACTION DONE (TICK BOX): ☐

BULKING UP MEALS WITH MORE PROTEIN AND VEGETABLES / SALAD

Eating more protein foods such as meat, fish, chicken, cheese, eggs, tofu, Quorn, pulses and vegetables will fill you up more and stop you feeling hungry. These foods also flatten out the post meal glucose rise and so help achieve the post meal glucose targets whilst avoiding dips in glucoses later.

ACTION DONE (TICK BOX): ☐

BEING ACTIVE AFTER EATING

Being active for 10-15 minutes after eating can make your post meal glucose level as much as 2 mmols/L lower and so help achieve the post meal glucose target.

This can be going for a walk or being active around the house or work place.

AVOID BEING INACTIVE IMMEDIATELY AFTER EATING

ACTION DONE (TICK BOX): ☐

AVOID EATING CARBOHYDRATE LATE IN EVENING

Overnight can be as much as a third of your day so getting glucose levels as near normal pre bed and overnight can really help optimise glucose levels for pregnancy.

Eating your evening meal before 7.30 pm and keeping evening snacks to minimal carbohydrate or carbohydrate free (unless eaten to avoid a hypo) can make all the difference to achieving the pre-bed, overnight and even fasting glucose targets.

ACTION DONE (TICK BOX): ☐

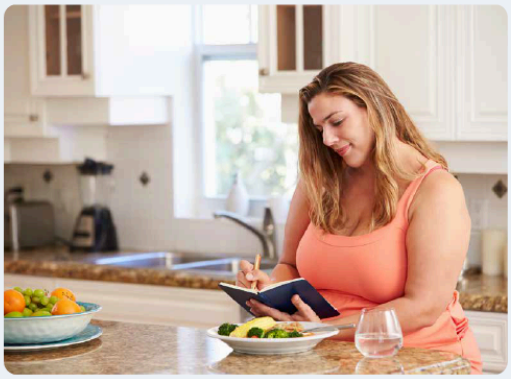
ACCURATE CARBOHYDRATE COUNTING

There are a number of useful resources to help with accurate carbohydrate counting:

- Carbs & Cals book or app (Chris Cheyette & Yello Balolia, Publisher - Chello)
- DAFNE Carbohydrate Portion List
- MyFitnessPal App
- Food Labels: use the "total carbohydrate" amount when working out how much carbohydrate is in the food.
- Restaurant's web sites: Nutritional information

ACTION DONE (TICK BOX): ☐

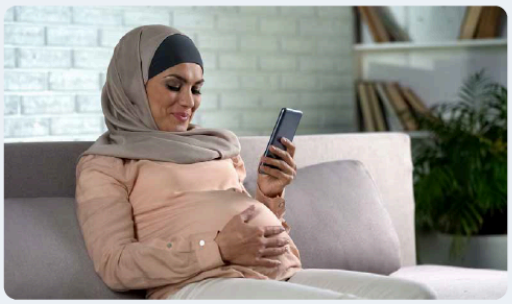
KEEP A FOOD DIARY



Keeping a food diary can help you learn what meals and carbohydrate choices are working well for you keeping those post meal glucoses in target. It can also help you see which choices are best avoided.

ACTION DONE (TICK BOX): ☐

STAY IN TOUCH

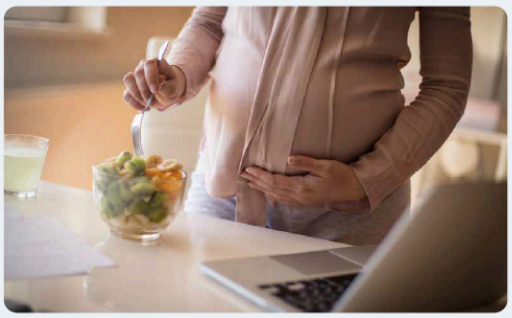


It can be challenging to keep up with changes in insulin requirements as your pregnancy progresses

Women who are in regular contact with the diabetes educators report better glucose levels and feel in better control.

ACTION DONE (TICK BOX): ☐

SNACKS



Snacking mid meal can be really helpful to avoid post meal hypos, help manage hunger and optimise nutrition.

Making snack choice healthy, high in fibre and avoiding refined forms of carbohydrate really helps keep glucose levels stable between meals.

Good types of carbohydrate snacks are: fruit, yogurt, whole wheat crackers & oatcakes with protein toppings. Additional lists are available from clinic.

It can feel tempting to go for sweeter more refined carbohydrates especially if trying to avoid a hypo but these foods, even if covered with insulin, make it difficult to keep the next pre meal glucose in target.

ACTION DONE (TICK BOX): ☐

Carbohydrate Choices

This table lists foods that many pregnant women with diabetes have found result in glucose levels above target post-meal. The 'try instead' list suggests some alternatives that can work well.

REFINED CARBOHYDRATES TO AVOID (High glycaemic index (GI))	TRY INSTEAD (Low glycaemic index (GI))
All white breads: loaf, rolls, pitta, naan, non-traditional baguette, croissant, chapattis, Panini, wraps.	**High fibre breads:** Rye bread and sourdough bread have the lowest GI. Whole-wheat, stoneground, granary and multi-grain varieties of breads have lower GIs. Chapattis made with whole meal flour Freezing bread first can help lower the GI
White flour based foods: Cakes, biscuits, cream crackers, water biscuits, Ritz, Tuc, Yorkshire pudding, dumplings, pizza, pastry (pies, pasties, quiche, sausage rolls, spring rolls). Breaded & battered foods e.g. fish fingers, battered fish	Oatcakes Whole-wheat crackers & crisp-bread e.g. Ryvita, Cracker wheat. Wheatmeal Digestives, Hobnobs, Hovis biscuits (one or two)
Low fibre & sugar coated breakfast cereals: Cornflakes, Rice Krispies, Special K, Sugar Puffs, Cocoa Pops, sweetened muesli.	**High fibre cereals:** Jumbo oats Most women don't tolerate any cereal in pregnancy. You may tolerate small amounts of some high fibre cereals earlier in pregnancy (up to 20 weeks): All Bran, Bran Buds, Shredded Wheat See breakfast guidance
Rice, pasta, grains: No types need to be avoided.	The best rice is basmati. Brown rice & whole-wheat pasta may give benefit. Cooling rice, pasta and potato after cooking and then eating cold or re-heating will lower the GI Couscous, bulgur wheat, semolina, tapioca, quinoa
Processed potato products: Oven chips, French Fries, Smiley faces, waffles, Croquettes, frozen roast potatoes, instant potato, ready meals with instant potato topping	**Home cooked potatoes:** Boiled is best Lightly mashed (non-instant) Small baked potato, Sweet potato, yam, cassava
Processed savoury snacks: Hula Hoops, Quavers, Pringles, Monster Munch, French Fries, Skips, baked crisps	Sliced potato crisps (e.g.Walker's or Kettle crisps) Ryvita snacks Vegetable crisps Salted or natural popcorn
Cold drinks: Fruit juices, smoothies, full sugar squash and fizzy drinks Lucozade	Water. Sugar free squash, sugar free carbonated drinks. DASH water. Soda water.
Sugar: Sugar, glucose, maltose, dextrose, honey, treacle and syrup	Artificial sweeteners if a variety are used and in small quantities Splenda, Sweetex, Hermesetas, Nutrasweet, Candarel, Stevia
Preserves/spreads: Jam, marmalade, honey, lemon curd, maple syrup, chocolate spread	Marmite, Vegemite, nut butters such as peanut butter

Continued over the page

✕ REFINED CARBOHYDRATES TO AVOID (High glycaemic index (GI))	✓ TRY INSTEAD (Low glycaemic index (GI))
Sweets / desserts: Melon, mango, pineapple(some people may tolerate small portions), Dried fruit Sweets, chocolates, mints Sweet puddings Tinned fruit in syrup	Fresh fruit, frozen fruit, tinned fruit in natural juice (juice drained off) Sugar free Jelly Yogurt: natural, Greek-style, Icelandic style (high protein such as Skyr), fruit yogurt (under 15g total carbohydrate per portion or pot) 70% cocoa solids chocolate Full fat ice cream (no added biscuits/caramel ripple/etc.)
Condensed, evaporated milk	Crème Fraiche, cream
Ready meals/stir in sauces/take away: Some ready meals & sauces contain significant amounts of sugar for example sweet & sour sauces, jar or packet Chinese sauces, Chinese takeaway, tomato soup, baked beans, tinned spaghetti	Reduced sugar baked beans (drain off as much sauce as possible)
Bed-time & Malted drinks such as Ovaltine, Horlicks, drinking chocolate.	Cadbury's Highlight, Ovaltine Options, cocoa powder.

DTN UK | Top tips: Using Dexcom G6 real-time CGM in pregnancy

WELCOME

ℹ This leaflet has been written to complement the information you will get during your sensor training. The Dexcom G6 sensor is approved for insulin dosing decisions and doesn't require fingerstick calibrations.

ABOUT THE SENSOR

Your sensor sits just under the skin and measures the glucose in the fluid around the cells every minute. The sensor glucose measurement may be 5-10 minutes behind what the blood glucose is reading.

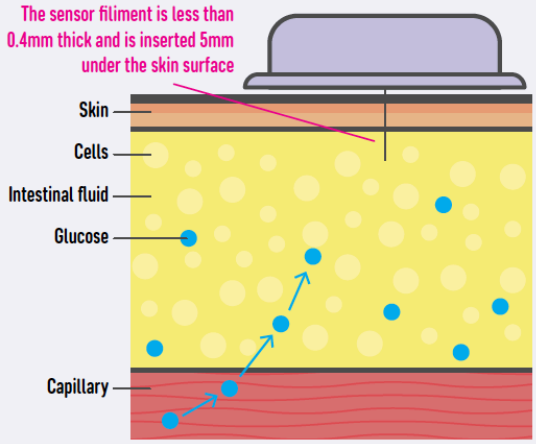
The sensor glucose can be displayed in three ways:

1. Glucose reading now
2. Glucose direction which can be:

steady (grey) rising (yellow) or falling (red)

3. Glucose history (previous 1, 3, 6, 12 or 24 hours)

The sensor sends glucose data to your mobile phone (and sometimes a smart watch) using the Dexcom Clarity App. If your phone is not compatible with the G6 App we can provide you with a receiver.

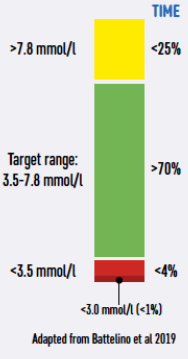


REVIEWING SENSOR GLUCOSE LEVELS

TIME IN RANGE gives a good overall picture of your sensor glucose levels over a 1-2 week time period. Most women start pregnancy with around 50% Time in Range, aiming to get to 70% as soon as possible. It may take until 20-24 weeks of pregnancy, and a **lot of attention to carbohydrate choices and timing of pre-meal insulin** doses to achieve your glucose targets.

- More than 70% (16hrs 48mins/day) Time in Range 3.5-7.8 mmol/L
- Less than 25% (6hrs/day) above 7.8 mmol/L
- Less than 4% (1hr/day) below 3.5mmol/L
- Less than 1% (15 mins/day) below 3.0 mmols/L

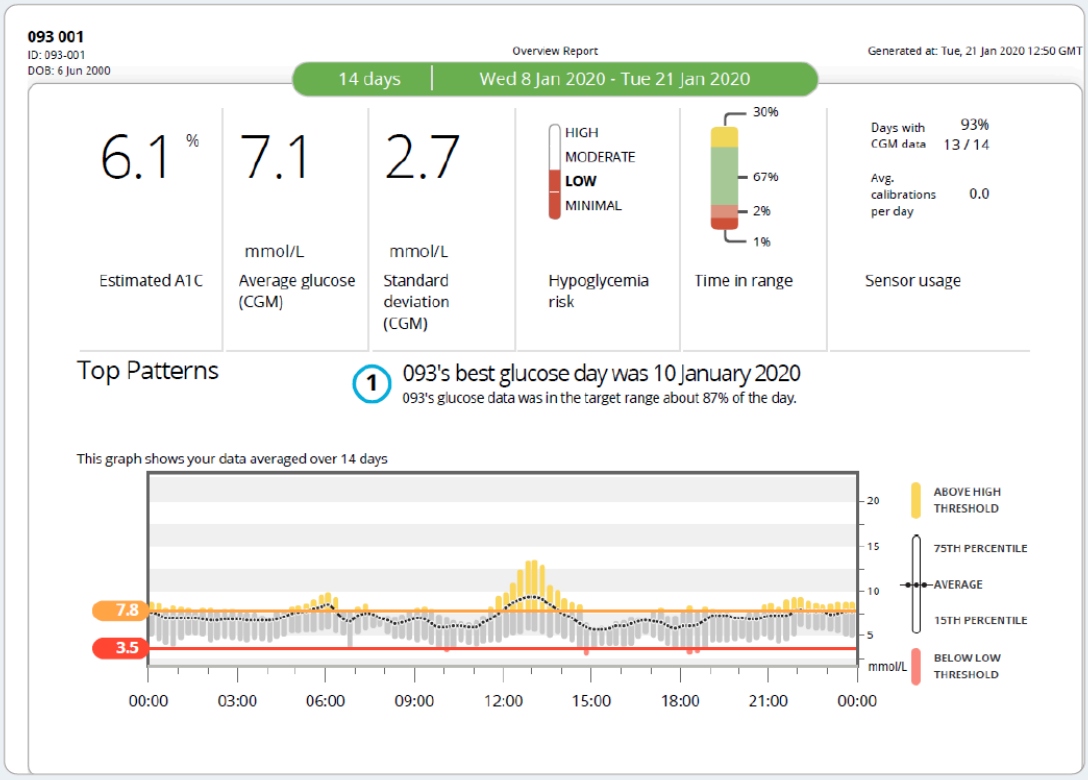
ℹ **Every extra 5% Time in Range has benefits for you and your baby!**



Adapted from Battelino et al 2019

CONSIDERATIONS WHEN STARTING GLUCOSE SENSORS IN PREGNANCY:

- Be prepared to see many more glucose readings out of target!
- It is important **not to overreact** to readings which are above target with aggressive **correction doses** of insulin. Remember insulin takes time (typically 3-4 hours) to lower above target glucose levels so **don't correct in the first 2 hours after eating!**
- When your glucose levels are above target, reflect on what might have caused the increase?
  - under-estimating or eating **too much carbohydrates** (very easy to do with rice, pasta and potato meals),
  - quickly absorbed carbohydrate choices (e.g. most breakfast cereals, shop bought sandwiches, white flour products),
  - not injecting your pre-meal insulin bolus early enough before eating (aim for at **15±5 mins before eating in trimester 1, 30 ±10 mins in trimester 2 and 45±15 mins in trimester 3**)
- Steady or gentle changes in glucose indicate that your carbohydrate choices and timing of insulin bolus doses are working well
- Some women choose to set a high alert for 10mmol/L or 12mmol/L – entirely optional
- The **Urgent Low Alarm** is set at **3.1mmol/L** and cannot be turned off. **This is for your safety!**
- Sharing your sensor data means that that you and your diabetes team can review your glucose patterns at every clinic appointment. The data shared does not include your name/personal details



WHEN TO DO FINGER STICK CHECKS:

- To confirm hypoglycaemia and monitor recovery from a hypo
- If the sensor reading doesn't match how you feel or the glucose you were expecting
- If the sensor is not working

There are times when the sensor glucose data may be less reliable and you might want to do some finger stick checks, for example during

- the first 24 hours of new sensor
- times of rapidly changing glucose levels (following recovery from a hypo)
- moderate exercise or activity

AVOIDING HYPOGLYCAEMIA

In pregnancy, you may find your symptoms of hypoglycaemia become more subtle and sometimes disappear. Being able to check your glucoses more frequently and using the directional arrows on your sensor can be helpful. The **Urgent Low Alarm** is set at **3.1mmol/L**. This cannot be turned off.

Established sensor users sometimes set an Urgent Low Soon Alert: this alerts 20 min before sensor glucose predicted to reach 3.1 mmol/l, giving more time for hypo prevention. Others prefer to set a higher personalised Low Glucose Threshold Alert between 3.5-4.5 mmol/L. These alerts are optional but early treatment with 5-10g of carbohydrate (sometimes called "micro-carbs") can raise glucose by 1-2 mmols/L and may help you to prevent a hypo event.

Directional Arrows	**Over past 15 minutes your glucose has been**	**If this trend continues how will glucose change?**		**Hypoglycaemia avoidance and treatment suggestions**	
		How long to change by 1 mmol/l?	**In 30 minutes**		
	Slowly falling	10 mins	2-3 mmol/L		1 GlucoTab or 1 jelly baby = 4g carb
	Falling	5-7 mins	3-5 mmol/L		2 GlucoTabs or 2 jelly babies = 8g carb
	QUICKLY FALLING	Less than 5 mins	Up to 5mmol/L **ACT NOW!**		3-4 GlucoTabs or 3-4 Jelly babies = 15g carb*

- Remember your **sensor glucose may be 5-10 minutes** behind your blood glucose level and can remain low even when your blood glucose is back in range. Using sensor glucose to monitor recovery from hypoglycaemia may result in over treatment of hypoglycaemia.
- **200mls of orange juice** or **1 Lift (Formerly GlucoJuice) drink** contain 15g carb raise glucose levels quickly and **work well for hypo treatment**.
- Always use a finger stick glucose to confirm hypoglycaemia and monitor recovery from a hypo
- During pregnancy, most hypos occur between meals (1-4 hours after eating). These are caused by a mismatch between **quickly absorbed carbohydrates** and **slowly absorbed pre-meal insulin**.
- Frequent between meal hypos indicate that your carbohydrate choices and timing of insulin doses may not be working so well. Ask your diabetes team for advice!

CORRECTING:

Post meal: It is not recommended to correct glucose readings above target within 2 hours of eating as this can result in a low glucose later.

At 1 hour: If your glucose is reading above target and or with upward trending arrows reflect on what might have caused this and can it be avoided in the future? Think about the type of carbohydrate, amount of carbohydrate, insulin timing and your activity levels. 10-15 minutes of post-meal activity (walking, housework etc) will speed up insulin absorption and lower your glucose levels

At 2 hours: If sensor glucose is the same or higher AND is either stable (no arrows) or rising (upward arrow) then it is reasonable to give a correction dose. Pump users should use the bolus advisor (which takes account of the insulin on board). If using injected insulin, ask for a bolus calculator device (e.g Expert meter) to calculate your correction dose. Alternatively, you can give half of your usual correction dose,

Do not correct if sensor glucose is falling (any downward arrow).

If you are unwell, have glucose levels above 12mmol/L or have ketones then follow your Sick Day Rules.

TROUBLESHOOTING

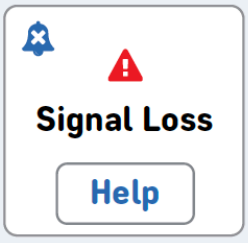
- **Keep the sensor packet** until the sensor has been used effectively and removed. If the sensor ends early or falls off make a note on the packet and bring the lid with the lot number to your next clinic appointment
- If the sensor does not deploy properly and the needle doesn't retract then bring the whole device back in the packet and your study team will provide replacements

SENSOR SIGNAL LOSS

Sensor signal can occasionally drop out and should automatically reconnect. If it doesn't try

- Turning your Bluetooth off and on again. Turning your phone off and on again can also help.
- If still not reconnecting make a note of the transmitter ID. Enter a fake ID starting with 8 (for example 8YYYYY) and allow the system to search for it. Then re-enter the correct transmitter ID and it should automatically reconnect.
- If you have persistent signal loss contact the study team

Always keep a finger stick meter with you. Don't rely 100% on the sensor glucose levels



SKIN CARE

The sensor should stay securely attached to your skin using its own adhesive. Some women find adhesive barrier wipes (Skin Tac™) helpful to improve skin "stickiness", others use overlay patches or medical tape around the edges of the adhesive patch (making sure not to cover the transmitter). Medical adhesive removers (Lift Plus) can help to remove residual adhesive. Your study team can supply these for you to try.

LABOUR & DELIVERY

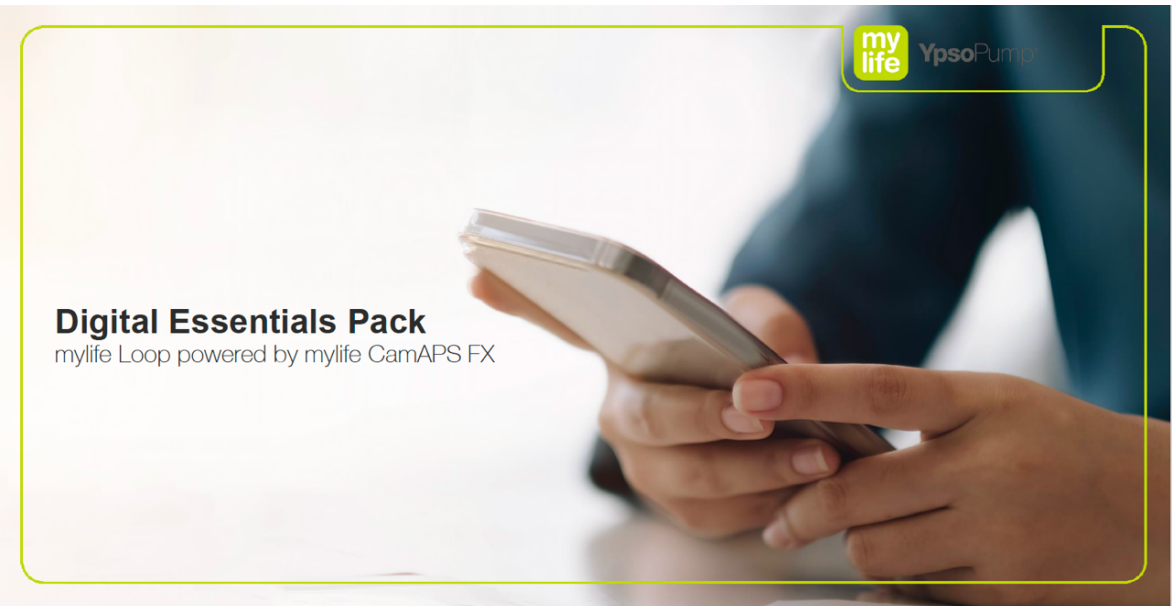
More and more women continue sensor use during antenatal hospital admissions, after steroids and throughout labour and delivery. Midwives may not always be familiar with sensors and may take additional glucose measurements on hospital meters for their records. Your research team will provide written guidance for obstetric teams so that you can be supported to continue sensor use in hospital

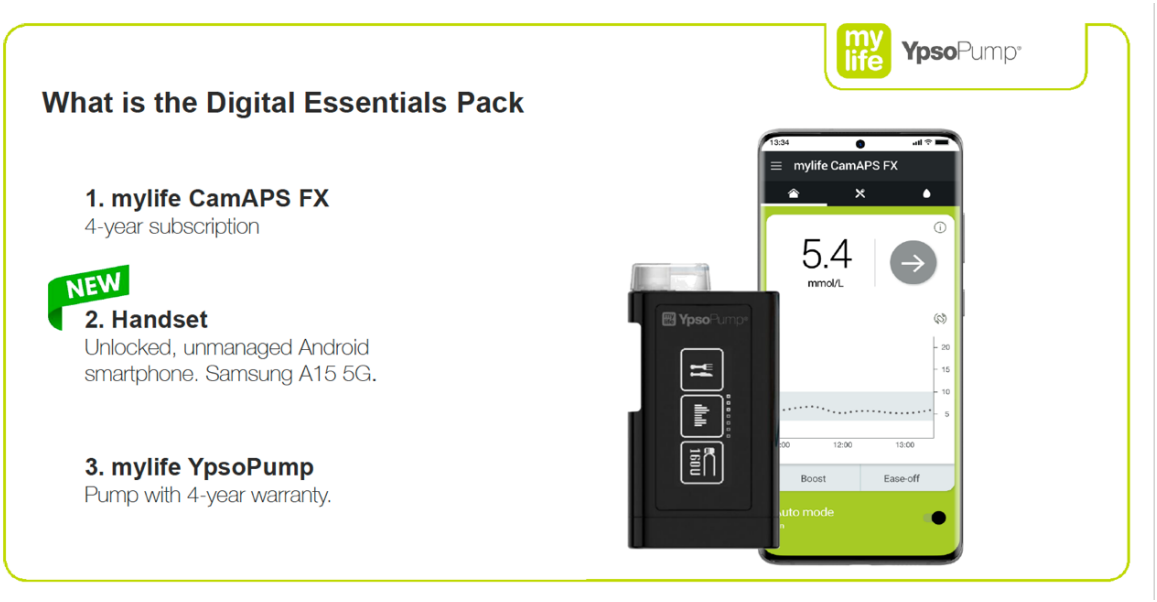
Pages 6-10 of this leaflet are the same as pages 2-6 of the DTN UK | Top tips for optimising glucose levels in pregnancy information leaflet

Appendix 5 Digital Essentials Pack

Appendix 5.1 Dana CamAPS FX Android smartphone package

Appendix 5.2 mylife CamAPS FX digital essentials pack





Who is it for?

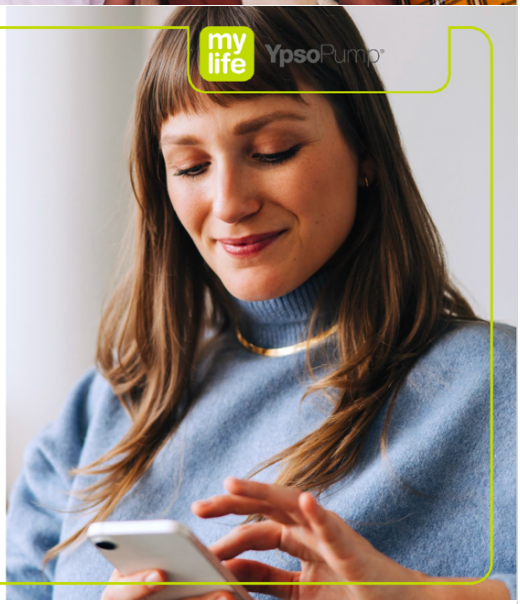
Everyone.

Approved for people with type 1 diabetes aged 2+ when used with Dexcom G6 or 4+ when used with FreeStyle Libre 3.

Funding will be available for anyone who doesn't have a compatible phone, meaning:

- ✓ Anyone who doesn't have a compatible phone including iOS users
- ✓ Anyone who doesn't have a phone

In pregnancy



Priority should be given in pregnancy, where:

- ✓ CamAPS FX is the only algorithm licensed and effective for use
- ✓ Pump starts need to happen as soon as possible

For further information on the AiDAPT trial that evidenced 10.5 % more time spent in the pregnancy specific range of 3.5–7.8 mmol/L, please click the button below.

Click here to read more on the AiDAPT trial

Options available to order:

Two options available on NHS Supply Chain

Product code	Product description
MYLDEP01	mylife Loop powered by mylife CamAPS FX Digital Essentials Pack (handset included) ✓ mylife YpsoPump ✓ mylife CamAPS FX ✓ Handset
700009424 & MYLOK	mylife Loop powered by mylife CamAPS FX (no handset included) ✓ mylife YpsoPump ✓ mylife CamAPS FX

Why is this important?

The NICE TA is a transformative update to health legislation that will increase access to technology for people with type 1 diabetes. This increase in access will improve outcomes and improve quality of lives.

Echoing the ethos of the NICE TA, the Digital Essentials Pack is another example of NHS England and NHS Supply Chain working with industry and the available technology to break down barriers to access.

The NHS paying for a phone is unprecedented – it's not a medical device, neither is there a process for listing a phone in supply chain. This has all had to be trailblazed to make room for the Digital Essentials Pack.

It's a radical and progressive policy change to increase access to mylife Loop which is going to have a significant impact for the type 1 diabetes population as a whole.

When will it be launched?

NHS England

Within the NHS on the 8th October:

- ✓ Presentation and written comms from NHS England
- ✓ Overview and FAQ document sent to all trusts from Leigh Carr
- ✓ Presented during HCL webinar

world diabetes day

To the public on 14th November, World Diabetes Day. Messaging focus:

- ✓ Impact in pregnancy
- ✓ Impact on deprivation
- ✓ Impact on access to HCL

Key messages

1. **Focus on access equality** – The Digital Essentials Pack ensures that all patients who need it, regardless of financial situation, have access to HCL technology. This project is a landmark move by the NHS to address access inequality in digital health and echoes the ethos of the NICE TA on HCL.
2. **Improving patient outcomes** - By offering the Digital Essentials Pack, we hope to see better management, better quality of lives, and improved health outcomes for people with type 1 and their caregivers.
3. **Improve outcomes in pregnancy** – As evidence by the AiDAPT trial, it is recommended that mylife CamAPS FX is used during pregnancy. This initiative eliminates the barrier of needing to purchase a smartphone, ensuring that their therapy and health outcomes are not compromised. Pregnancy is time critical, and the sooner they get access to a licensed and effective algorithm, the higher the chances are of better outcomes.
4. **Collaboration -** This project highlights the power of collaboration between industry, NHS England, and NHS Supply Chain. Willing people working together for a greater good.

Frequently asked questions

What phones will the patient receive?	A Samsung A15 5G. (as of November 2024). The choice of phone has been agreed upon by mylife Diabetescare, CamDiab and NHS England. We have balanced cost against future-proofing to ensure the phone stays for as long as possible. The phone option may change as different technology becomes available.
Can they use these phones as their personal phones?	The patient is free to use the phone as they wish, however we would encourage that they keep it solely for the use of housing the mylife CamAPS FX app.
Are the phones covered by insurance?	No. The phones will not come with insurance. The patient will be encouraged to take out their own insurance. Insurance of these devices is low cost at around £2 per month. If the phone is lost, stolen or damaged, the patient will be responsible for replacing it. This will be discussed in their pump start and included in the training checklist.
Are the phones covered by a warranty?	No. The phones do not have a warranty. mylife Diabetescare will provide no customer support. If a phone stops working, the patient will be directed to the phone manufacturer. This will be discussed in their pump start and included in the training checklist.

Frequently asked questions

What happens if the phone becomes incompatible with the app?	We have done what we can to mitigate against this by selecting a phone which is reasonably new, and we feel won't fall off the compatibility list of the app or either of the CGM sensors. With the launch of the iOS version of the mylife CamAPS FX app, we suspect that those affected will be limited and we will deal with that problem if it arises.
What should the user do if they no longer need the phone?	mylife Diabetescare will send the user a free-post envelope to return the device. The device will be returned to a pool of phones used for goodwill purposes within the NHS. The decision to return the phone is entirely at the discretion of the user but is encouraged so the device can be used to help others. This is entirely optional, and there is no responsibility on the HCP to track or monitor this.
Who should receive the Digital Essentials Pack?	Those who do not have a compatible phone (those without a mobile phone, those with a non-compatible Android device, and for those with an iOS device). Priority should be given to anyone who is pregnant or planning a pregnancy.
Who will set up the phone and install the app?	The patient will be responsible for setting up the phone and downloading the app prior to the pump start.

Frequently asked questions

Does this change the process for the mylife CamAPS FX patient training?	No. The process will remain the same in that prior to the pump start the patient should complete the CamAPS FX training that generates their training code. From the 5th of November, this will be in-app. Before the 5th of November, this will be done online via the CamDiab taining portal.
Who should not receive a phone?	Anyone who has a compatible Android phone for use with the mylife CamAPS FX app.
When will the iOS version of the mylife CamAPS FX app become available?	Availability is aimed for the first half of 2025.
Will the phones come with a SIM card and / or data plan?	No. For the mylife CamAPS FX to function, no data is required. The HCL system operates via Bluetooth so no data is needed. For therapy data to be sent to the cloud (for example, Glooko) we would encourage people to connect the device to their home / school / work WiFi to continue data sharing throughout the day.

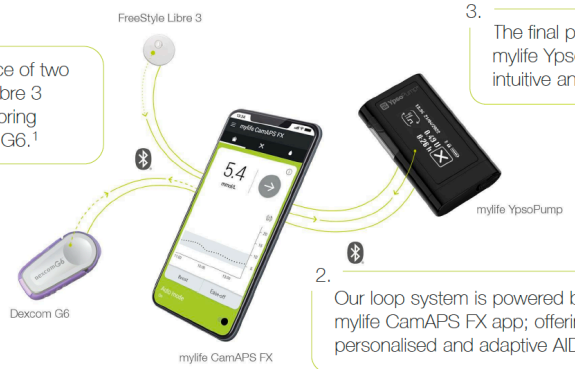
Frequently asked questions

When will the patient receive the phone?	The patient will receive the phone prior to the pump start to enable them to set up the phone themselves. It will be their responsibility to set up the device, download the mylife CamAPS FX training, and to do the CamDiab training.

mylife Loop powered by mylife CamAPS FX

For HCL you need a CGM sensor, a pump and an algorithm. The sensor sends glucose data to the mylife CamAPS FX app which then adjusts insulin delivery on the insulin pump.

1. mylife Loop offers the choice of two CGM sensors: FreeStyle Libre 3 Continuous Glucose Monitoring System (CGM) or Dexcom G6.[1]



2. Our loop system is powered by the mylife CamAPS FX app; offering personalised and adaptive AID

3. The final piece of the system is the mylife YpsoPump itself. A simple, intuitive and discreet insulin pump.

POWERED BY CamAPS FX

1. Dexcom and Dexcom G6 are registered trademarks of Dexcom, Inc. in the United States and/or other countries. The sensor housing, FreeStyle, Libre, and related brand marks are marks of Abbott and used with permission.

Key benefits

Customisable
Personalised glucose target from 4.4mmol/L to 11mmol/L.

Programmable
Boost and Ease off modes to support illness and exercise.

Adaptive
Algorithm considers 3 insulin requirements; daily, day-to-day and mealtime insulin, making it highly adaptive to your routine.

Discreet
Control the system, including bolus delivery, from your smartphone

For everyone
Indicated for use from 2 years and over, and for use in pregnancy.

Simple
Algorithm only requires TDD and weight (kg) for set up.

For further information

For product and / or service questions, please email

info@ypsomed.co.uk
or, contact your local area representative

For procurement questions, please email NHS England at

urninsulinpumps@supplychain.nhs.uk