NORWICH CTU

Automated insulin Delivery Amongst Pregnant women with Type 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	2.0
Date	5th December 2018
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	

This protocol has been written in accordance with current ISO 14155:2011 standard

Authorisation: Sponsor

Name	Emily Woodhouse
Role	Sponsor Representative
Signature	
Date	

Authorisation: CTU Director or Representative

Name	Professor Ann Marie Swart
Role	Norwich CTU Director
Signature	
Date	

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	

1 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, 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 competent authority 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. 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 $HbA1_c$ >10% (>86 mmol/mol). Women who enter pregnancy with HbA1c >10% (>86 mmol/mol) may participate if they achieve HbA1c ≤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 3.9-7.8 mmol/L based on CGM measures 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.

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
Emily Woodhouse	Norfolk and Norwich University Hospitals NHS Foundation Trust	Sponsor Representative
Laura Harper	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

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
Dr Goher Ayman	National Perinatal Epidemiology Unit	PPI Representative
Mrs Sarah Cains		PPI Representative

Professor Helen Murphy	UEA	Member

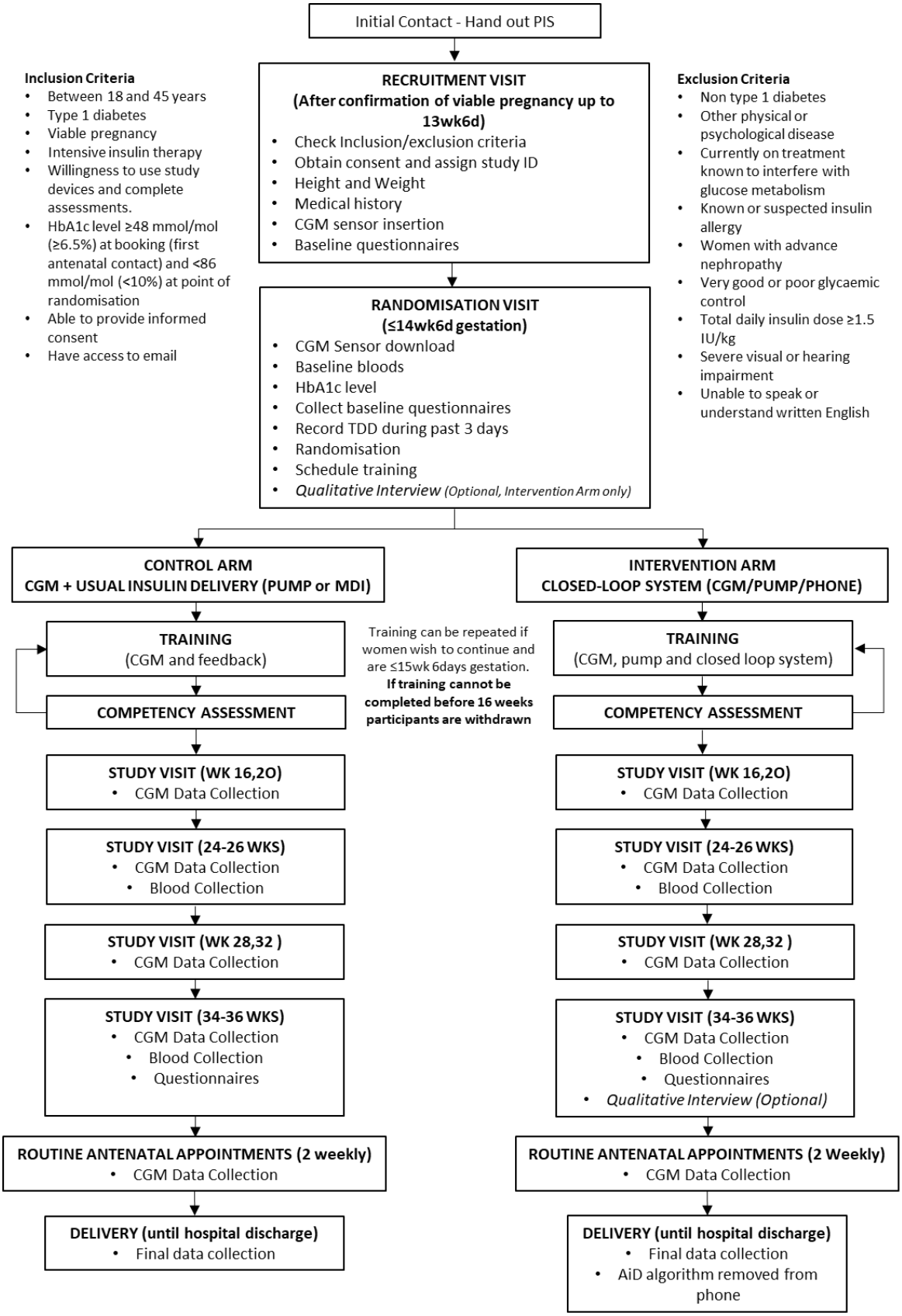
2.4.6 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Professor Jim Thornton	University of Nottingham	Independent Chair (academic obstetrician)
Dr Jackie Elliott	University of Sheffield	Independent Member (clinician)
Dr Debbie Cooke	University of Surrey	Independent Member (psychosocial)
Professor Graham Law	University of Lincoln	Independent Member (statistician)

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
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
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 (3.9-7.8 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 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 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, 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 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 of 3.9-7.8 mmol/L based on subcutaneous CGM measures.

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 of 3.9-7.8 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 NICE target range 3.9-7.8 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 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.

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.

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

The Medicines and Healthcare products Regulatory Agency (MHRA) require that details of all amendments including notification of new sites should be supplied to them and these amendments

cannot be implemented until a notice of no objection is received. Trial staff at NCTU will perform this task.

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, 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 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, 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.
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%). Women who enter pregnancy with HbA1c >86 mmol/mol (>10%) may participate if they achieve HbA1c ≤86mmol/mol (≤10%) before randomization.
7. Total daily insulin dose $\geq$ 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. Booster training sessions will also be offered to site staff after the first few participants have been recruited at a site.

6.3.1.5 Co-enrolment Guidance

Co-enrolment into interventional 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 (AiD) or to continue standard patient-directed insulin delivery (insulin pump or MDI), with CGM but without (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**). 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 continuous glucose monitor (CGM) (**Dexcom G6**). A CE marked real-time CGM system based on a subcutaneous glucose sensor.
- A 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 (**FlorenceX**). This will be uploaded onto a mobile phone which will be provided to the participants.

The investigational device (**FlorenceX**) 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 mobile phone with 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 removing the AiD algorithm before the participant is discharged from hospital after delivery. Participants will be able to keep the insulin pump and CGM system. NHS support for future use of these 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 treatment arm will receive training in the following:

- Continuous Glucose Monitoring (CGM) system
- Insulin pump
- Closed-Loop AiD system

Following completion of the training (prior to 16 weeks gestation) an evaluation of the participant's competency will be performed by the research team using a checklist of specific skills required to proceed. If competency in the use of the system is not demonstrated 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. 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.

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

Written protocols 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 glucose levels between 3.9-7.8 mmol/L during antenatal admissions and between 3.9-7.0 mmol/L during delivery.

After delivery (before maternal discharge) the study devices will be downloaded and the AiD algorithm removed from the phone.

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 patient-directed insulin delivery using either an insulin pump or MDI without AiD. Participants will use either their own smartphone (if compatible with the CGM software), or will be provided with a receiver 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 recorded at 4-weekly study visits.

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
    - Blood glucose targets and alarm settings

- Handling real-time CGM feedback including glucose trend arrows, reported high and low glucose
- Use of software to upload and interpret CGM data

Following completion of the training (prior to 16 weeks gestation) an evaluation of the participant's competency will be performed by the research team using a checklist of specific skills required to proceed. If competency in the use of the CGM system is not demonstrated 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. All Investigational devices will be marked 'for clinical investigation only' and sites will be instructed to keep these secure and separate from standard stock. Non-investigational devices provided will 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 take place, at least 4 weekly between 12 weeks until delivery.

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 analysis.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome is the percentage of time spent with glucose levels between 3.9-7.8 mmol/L based on CGM levels 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, mean CGM glucose and CGM glucose variability measures (CV, SD).
2. The frequency and severity of hypoglycaemia episodes defined as CGM glucose levels <3.5 mmol/L (level 1 hypoglycaemia) and <2.8 mmol/L (level 2 hypoglycaemia) for at least 15 minutes. Distinct episodes must be separated for at least 30 minutes.
3. The Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) measures
4. 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.
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 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. The mode of delivery (vaginal, instrumental, elective caesarean section and emergency caesarean section)
4. The gestational age at delivery and indication for any preterm delivery (<37 weeks)

5. Adverse events including pregnancy loss <24 weeks, stillbirth, neonatal death
6. Maternal hospital admissions (all admissions including the delivery admission)
7. 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 (breast, bottle, both)
5. Hospital length of stay (from delivery until hospital discharge)

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) (15)
2. The EQ-5D Health-Related Quality of Life Questionnaire (16)
3. Diabetes Distress Scale (DDS) (17)
4. Hypoglycaemia Fear Survey Questionnaire II (HFSQ II) (Worry scale only) (18)
5. Pittsburgh Sleep Quality Index (PSQI) (19)

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 3.9-7.8 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.

6.6 Participant Timeline

	Initial Contact	Recruitment visit	Randomization visit (Recruitment +1-2 weeks)	Training period	Routine antenatal appts (12, 16, 20 weeks)	24-26 weeks	Routine antenatal appts (28 and 32 weeks)	34-36 weeks	Delivery	Hospital discharge (infant)
PIS given out	X									
Check inclusion / exclusion criteria		X								
Obtain written informed consent		X								
Height and weight, medical history		X								
CGM data collection		Masked sensor inserted (7-10 days) and data downloaded			All participants wear CGM following completion of training. Data collected at each visit via receiver or smartphone					
Questionnaires		X	(confirm completed)					X		
Blood sample collection (5 mL) for future metabolic studies			X			X		X		
HbA1c level			X*			X		X		
Record average total daily dose during past 3 days		X	X		X	X	X	X	X	
Randomization			X							
Training and competency assessments			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		
!! Data Collection at Delivery									X	
Algorithm removed (intervention arm)									X	
# Infant Care and Feeding Data										X

! 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.

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)
- Masked Dexcom G6 sensor insertion

Women will have a subcutaneous glucose sensor (Dexcom G6) inserted by the clinical research team and will be instructed to wear it at home for 10 days. They will be asked to return for CGM sensor downloading within 14 days. Training and written instructions will be provided for the CGM.

6.6.1.2 Randomization Visit (Up to 15 weeks and 6 days gestation)

The following activities will be performed:

- CGM sensor download
- Baseline bloods
- Collection / confirmation of the completed baseline questionnaires
- Confirm HbA1c 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 by the research team 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.

6.6.1.3 Participant Training – Intervention Arm

(Post-randomization visit, with a maximum of 15 weeks and 6 days weeks gestation)

The device training for existing pump users randomized to AiD will take approximately 120 minutes for existing pump users 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.

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 (previous pump users) 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 will 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 participants 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.

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). 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.

6.6.1.5 Competency Assessment (Up to 15 weeks and 6 days gestation)

An evaluation of competency will be performed by the research team with a detailed check list of specific skills which women require to proceed with CGM / AiD. They must demonstrate competence in sensor insertion and interpretation of data (all participants), and in the technical management of the study insulin pump during manual and AiD modes (intervention participants). In addition, participants on the intervention arm will have their understanding of the management and response to AiD alarms evaluated. 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. Participants in the control arm will continue to use current methods of delivering insulin. The study CGM sensors will be used from recruitment until 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.

At these visits the following data will be recorded on the study database:

- Weight
- Blood Pressure
- 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 (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

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)

After delivery (before maternal discharge) the study devices will be downloaded and the closed-loop algorithm removed from the study phone.

In the event of early pregnancy loss in a participant on the intervention arm, the participant should be asked to return the smart phone to the research team at the earliest opportunity (via arranged post if this is more convenient for the participant).

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 (15). 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 (16) 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 (17). 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 (18). 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 (19) is a validated 19-item questionnaire that holistically assesses sleep quality and sleep duration over the preceding month.

6.6.3 Blood Sampling

Blood samples will be taken for the measurement of baseline HbA1c levels at sites. Less than 5 ml of whole blood will be taken from each participant and stored for subsequent metabolic studies.

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. 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 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 the follow-up schedule should return the smart 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 seen by 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 3 months following the last follow-up visit of the last patient randomized, 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 and are based on data from our previous studies of CGM and closed-loop in pregnancy (CONCEPTT and CLIP_03) (10, 20). During the pregnancy arm of CONCEPTT (an RCT of CGM in T1D pregnancy) women spent 52%±14% time-in-target at baseline (12±2 weeks), 50% ±13% at 24±2 weeks and 63%±15% at 34 weeks gestation. To detect a 10% absolute difference the time spent in the CGM target glucose range (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).

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 only remain in the trial for the duration of their pregnancy until first discharge home and, during this time 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 glucose 3.9-7.8 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
- Percentage time above target (> 7.8 mmol/l)

6.10.4.2.2 Other secondary endpoints

- HbA1c and average CGM glucose to quantify glucose control
- Percentage time spent with CGM ≥3.5 and ≤7.8 mmol/l to quantify time spent in the previous NICE guideline recommended target range
- 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 <2.8 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
    - <2.8 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 <2.8 (level 2) from CGM data defined as AUC <3.5 or AUC ≤2.8 for 15 minutes duration
- Nocturnal hypoglycaemia (NH): CGM glucose <3.5 (level 1) and <2.8 (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 time in target range, average CGM glucose, percentage time above target, percentage time below target, 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 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. 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 1st, 2nd and 3rd 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. Available case analysis method will be used for secondary outcome analyses in each time point.

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.

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.

6.10.4.8 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 Confounding

A sensitivity analysis will also be conducted for the primary endpoint if potential confounding factors collected at baseline will be detected.

6.10.4.9.3 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

Blood samples will be taken at 3 collection points to allow measurement of HbA1c levels.

In addition, up to 50 µL of plasma from each of the three collection points will be stored at -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

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. 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 serious 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 MHRA 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 study, SADEs must still be reported until delivery.

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 trial team (aidapt.trial@uea.ac.uk) at NCTU.

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, ethics committee and regulatory authorities.

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 in line with contractual requirements to enable their own vigilance reporting requirements.

All SAEs and device deficiencies which might have led to a SAE **which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other participants / users or other persons***, or a new finding to it must be reported to the MHRA by NCTU (or the CI) immediately, but not later than **2 calendar days** of NCTU becoming aware of a new reportable event or of new information in relation with an already reported event. All **other** SAEs and device deficiencies which might have led to a SAE, or a new finding/update to it, must be reported to the MHRA by NCTU (or the CI) immediately, but not later than **7 calendar days** of NCTU becoming aware of the a new reportable event or of new information in relation with an already reported event.

SAEs should also be reported to the main REC within 7 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.

NCTU will submit safety updates in accordance with the MHRA approval.

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

This Clinical Investigation Plan will be submitted to the national competent or equivalent authority (e.g. MHRA), as appropriate in each country where the trial will be conducted.

This is a Device Study and, as such, a Notice of Non Objection will be required form the MHRA prior to commencement of the trial.

The progress of the trial, safety issues and reports, including expedited safety reporting, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

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 or 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 both an MHRA Notice of No Objection and HRA approval is received and sites have either confirmed acceptance or, no objection has been received within the defined timescale. 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 delegate, 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. It is not intended that they will continue to use the closed loop system after the end of their participation in the trial.

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 ultrasound confirmation of viable intrauterine 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 v1.1; 4th 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.

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