Clinical Study Protocol

Protocol Number:	
ANZCTR Number:	12616000753459
Study Title:	**Hybrid Closed Loop Outpatient Trial**
Medical Device	MiniMed™ 670G
Protocol Version:	6.0
Funding:	**NHMRC/JDRF**

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Data Safety and Monitoring Board		
TBC	Trialist	To be appointed by the NHMRC clinical trials centre
TBC	Statistician	To be appointed by the NHMRC clinical trials centre
TBC	Clinician	To be appointed by the NHMRC clinical trials centre

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1. Study Synopsis: HCL Randomized Controlled Trial

Full title	Outpatient use of hybrid closed loop insulin management for type 1 diabetes, a multi-centre randomized controlled trial.
Short title	Hybrid Closed Loop (HCL)
Clinical Trial Phase	III
IND Sponsor (If Applicable)	N/A
Chief Investigators	Professor Timothy W Jones, Associate Professor Elizabeth Davis
Subject Number	12 – 25 yrs. n = 160
Summary of eligibility criteria	1. Type 1 diabetes (diagnosis consistent with American Diabetes Association Classification of Diabetes Mellitus) diagnosed at least 1 year ago 2. Fasting C peptide <0.1nmol/L (in the absence of hypoglycaemia) 3. Insulin regimen either: Multiple daily injections (MDI) ≥4 injections per day (≥3 rapid-acting insulin and ≥1 long-acting insulin), or insulin pump therapy (CSII) established for >3months. 4. Aged 12-<25years 5. HbA1c ≤10.5% 6. Living in an area with internet and cellular phone coverage 7. English speaking
Summary of exclusion criteria	1. Chronic kidney disease (eGFR <45mL/min/1.73m^2) 2. Use of any non-insulin glucose-lowering agent within the past 3 months 3. Oral or injected steroid use within the past 3 months 4. Pregnancy, or planned pregnancy within study period 5. Uncontrolled coeliac disease (not following a gluten free diet), or other untreated malabsorption 6. Uncontrolled thyroid disease 7. Clinically-significant gastroparesis 8. Uncontrolled hypertension (DBP >100 mmHg and/or SBP >160 mmHg) 9. History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack (TIA), stroke, or thromboembolic disease in the past 3 months. 10. Poor visual acuity precluding use of the investigational technology 11. Inability or unwillingness to meet protocol requirements (including carbohydrate-counting, CGM use as per allocated study group only). 12. Severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements
Study Design	HCL vs. standard therapy (MDI and CSII), Australian multicentre parallel design study. Participants will be randomized to use HCL or continue on standard therapy(MDI and CSII) Minimisation randomisation will be employed, stratifying by time in target glucose range 3.9-10 mmol/L, age, diabetes duration, and centre site.

	Duration of study – 7 months Enrolment period – 12 months
Investigational device	MiniMed™ 670G Insulin Pump Hybrid Closed Loop System.
Hypothesis	1. HCL will increase time in sensor glucose target range (3.9 – 10mmol/L) compared to standard therapy. 2. HCL will reduce time spent in hypoglycaemic range (<3.9mmol/L) compared to standard therapy. 3.HCL will improve glycaemic control as assessed by HbA1c. 4. HCL will have a positive impact on quality of life and fear of hypoglycaemia as determined by participant/parent questionnaires 5. HCL will be a cost effective intervention for the management of type 1 diabetes compared to standard treatment.
Primary objective	1. The primary objective is to compare the proportion of time spent in target glycaemic range (sensor glucose level 3.9 - 10 mmol/l) while using HCL or using standard therapy (MDI and CSII).
Secondary objectives	The secondary objectives are to compare the efficacy of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System versus standard therapy (MDI and CSII) by the measurement of the following: *1.Glycaemic(24hr, day (0600 – 2400), night (0000 – 0600))* CGM data will be collected in three time blocks; baseline (3 weeks CGM), 13 weeks (2 weeks CGM) and 26 weeks (3 weeks CGM) post randomisation. A sub analysis of HCL vs. MDI and HCL vs. CSII is planned. i. CGM data: a. % CGM Time <2.8 mmol/L b. % CGM Time <3.3 mmol/L c. % CGM Time <3.9 mmol/L d. % CGM Time 3.9-7.8 mmol/L e. % CGM Time >10.0 mmol/L f. % CGM Time >13.9 mmol/L g. % CGM Time >16.7 mmol/L h. Standard Deviation and Coefficient of Variation of CGM values i. Mean CGM glucose ii. Average Fasting blood glucose (mmol/L), as measured during the three CGM time blocks at baseline, 13 weeks and 26 weeks. Defined as fasting capillary blood glucose level on waking (between 5am and 9am), at least 6 hrs after an insulin bolus for carbohydrate. iii. Average Glycaemic control as measured by HbA1c collected at baseline, 13 weeks and 26 weeks post randomisation. iv. Hospitalisations rate for diabetic ketoacidosis over the 7 month study period. v. Episodes of severe hypoglycaemia over the 7 month study period (defined having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or i.v.glucose).

2. Clinical measures

The compare the difference between HCL insulin delivery vs standard therapy for the following measures

i) Change in auxological parameters (height, weight)
ii) Change in total daily dose , including basal and bolus proportion, carbohydrate ratios and insulin sensitivity

3. Psychosocial:

Questionnaires will be conducted on 3 occasions: at baseline, 13 weeks and 26 weeks.

i. **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*
ii. **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*
iii. **Anxiety***: State-Trait Anxiety Inventory (Child version for 12-15yrs, adult version ≥16-<25yrs)*
iv. **Impact and Satisfaction***: The Diabetes Treatment Satisfaction Questionnaire status and change version (16 - <25years)*
v. **Quality of Life***:12-<25years: EQ-5D-Y,*
vi. **Diabetes specific quality of life***: PedsQL –Child version (12 year olds), Adolescent version (13 – 18) and young adult version (18 – <25).*
vii. **Diabetes distress:** *Problem Areas in Diabetes (Teen version for 12 – 17 years, standard version ≥17-<25yr)*
viii. **Participant reported outcome for Automated Delivery system:** INSPIRE Questionnaires : baseline and post-assessment versions Child version (12 year olds), Adolescent version (13-18) and adult version(18-25)
ix. **Semi structure interview** (all ages – post study, PCH only)

4. Human-technology interaction:

To assess participant technology interaction and explore adherence patterns and approaches that may improve it. Repeated sampling methodology will be used. A series of questions will be asked once a week via a phone app, which will take less than 1 minute to complete.

5. Health-economic

To assess the health economic impact of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System vs standard therapy (MDI and CSII). The following data points will be used as part of the economic analysis:

i. QALYs calculated from the EQ-5D
ii. Hypoglycaemic events and HbA1c
iii. Participant reporting on work interruption
iv. Investigator reporting time spent on training, education and

	support, by the type of health professional resource used v. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin). *6. Biomarkers (*all ages) To assess the impact of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System Vs standard therapy (MDI and CSII) on the biomarkers listed below. Biomarkers will be tested from blood and urine samples at baseline, and 26 weeks post randomisation. i. Cell Adhesion Molecules (CAM)S ii. Soluble vascular cell adhesion molecules sVCAM iii. Soluble intercellular adhesion molecules sICAM iv. s-e Selectin v. Oxidized Low density lipoprotein vi. Myeloperoxidase. vii. MicroRNA signatures for arterial, renal and retinal complications viii. Telomerase ix. DNA methylation/acetylation x. Glycomark xi. Isoprostanes and proteomics xii. Clotting profile *7. Performance Parameters* To assess the performance of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System, and components. The following measures will be used: i. Proportion of time hybrid closed loop is active ii. Unplanned exits from closed loop (*n*) iii. Sensor performance – mean absolute relative difference (MARD), sensor failures (*n*) iv. Insulin delivery line performance – reported delivery line failures (*n*) *8. Health Care Providers experiences* To assess health care providers experiences and expectations of Hybrid Closed Loop insulin delivery.
Primary endpoint	The % time sensor glucose is in target range (3.9–10 mmol/L) during HCL insulin delivery vs standard therapy (MDI and CSII), measured 23-26 weeks post-randomisation.
Secondary endpoints	1. *Glycaemic*: i. CGM data: a. % CGM Time <2.8 mmol/L b. % CGM Time <3.3 mmol/L c. % CGM Time <3.9 mmol/L d. % CGM Time 3.9-7.8 mmol/L

e. % CGM Time 3.9-10.0mmol/L
f. % CGM Time >10.0 mmol/L
g. % CGM Time >13.9 mmol/L
h. % CGM Time >16.7 mmol/L
i. Standard Deviation and Coefficient of Variation of CGM values
j. Mean CGM glucose

ii. Average Fasting blood glucose (mmol/L), as measured during the three CGM time blocks at baseline, 13 weeks and 26 weeks post randomisation. Defined as fasting capillary blood glucose level on waking (between 5am and 9am), at least 6 hrs after an insulin bolus for carbohydrate.
iii. Average Glycaemic control as measured by HbA1c collected at baseline, 13 weeks and 26 weeks post randomisation.
iv. Hospitalisations rate for diabetic ketoacidosis over the 7 month study period.
v. Hospitalisations rate for severe hypoglycaemia over the 7 month study period.

A subanalysis of HCL vs. MDI and HCL vs. CSII is planned.

2. *Clinical measures*

The difference between HCL insulin delivery vs standard therapy for the following measures

i. Change in auxological parameters (height, weight)
ii. Change in total daily dose , including basal and bolus proportion, carbohydrate ratios and insulin sensitivity

3. *Psychosocial:*

i. **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*
ii. **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*
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vii. **Diabetes distress:** *Problem Areas in Diabetes (Teen version for 12 – 17 years, standard version ≥17-<25yrs)*
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ix. **Semi structure interview** (all ages – post study, PCH only)

4. <u>Human-technology interaction:</u>

Describe participant technology interaction, adherence patterns and approaches that may improve it.

5. <u>Health-economic</u>

Report the health economic impact of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System Vs standard therapy (MDI and CSII). The following data points will be used as part of the economic analysis:

i. QALYs calculated from the EQ-5D
ii. Hypoglycaemic events and HbA1c
iii. Participant reporting on work interruption
iv. Investigator reporting time spent on training, education and support, by the type of health professional resource used
v. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin).

6. <u>Biomarkers</u>

Assess the difference between MiniMed™ 670G Insulin Pump Hybrid Closed Loop System vs standard therapy (MDI and CSII) after 26 weeks of treatment on the following biomarkers:

i. Cell Adhesion Molecules (CAM)S
ii. Soluble vascular cell adhesion molecules sVCAM
iii. Soluble intercellular adhesion molecules sICAM
iv. s-e Selectin
v. Oxidized Low density lipoprotein
vi. Myeloperoxidase.
vii. MicroRNA signatures for arterial, renal and retinal complications
viii. Telomerase
ix. DNA methylation/acetylation
x. Glycomark
xi. Isoprostanes and proteomics
xii. Clotting profile

7. <u>Performance Parameters</u>

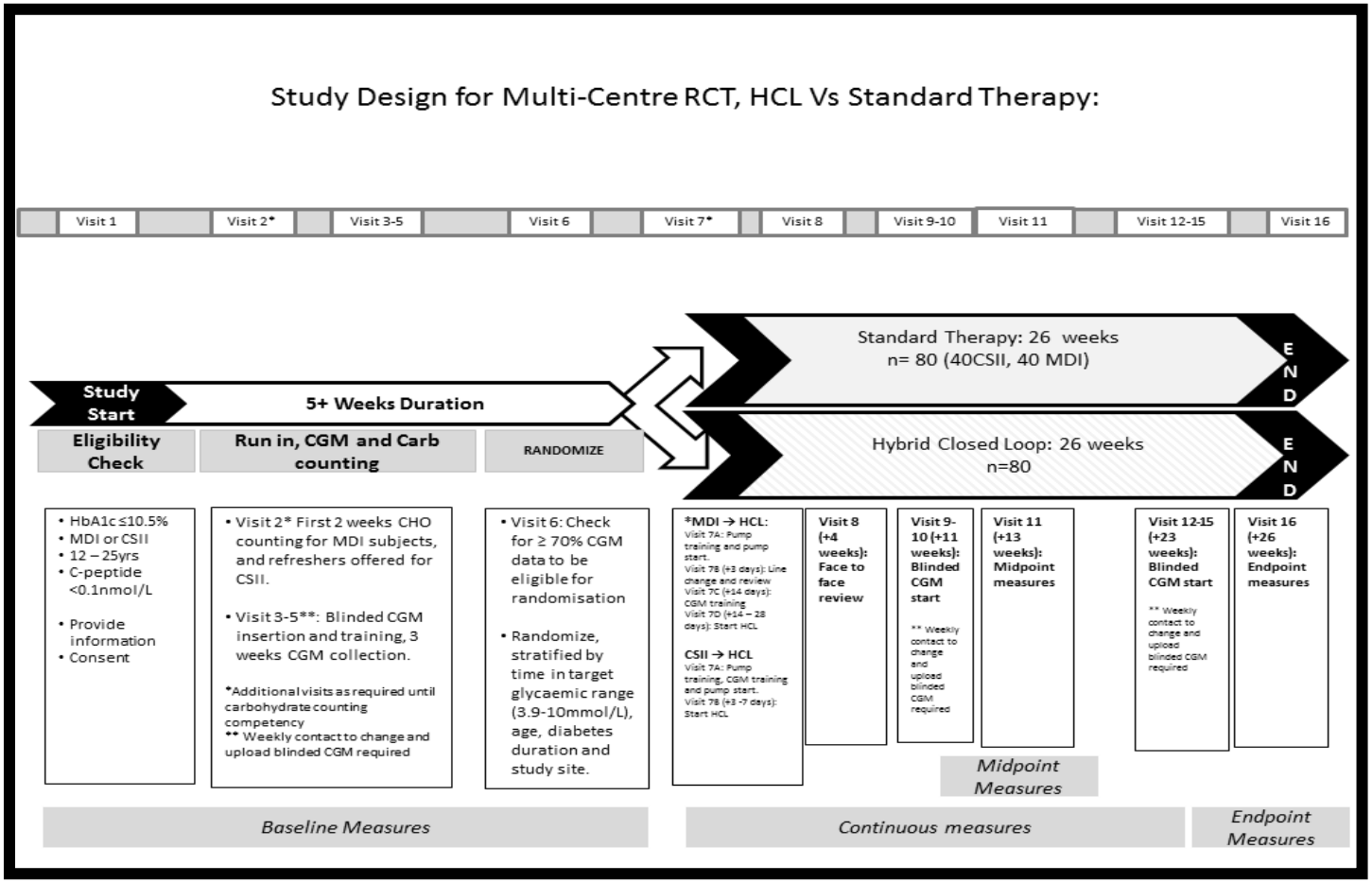
To report the performance of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System, and components. The following measures will be used:

i. Proportion of time hybrid closed loop is active
ii. Unplanned exits from closed loop (*n*)
iii. Sensor performance – mean absolute relative difference (MARD), sensor failures (*n*)

	iv. Insulin delivery line performance – reported delivery line failures (*n*) *8. <u>Health Care Providers Experiences</u>* To report health care providers experiences and expectations of hybrid closed loop systems through the study duration
Baseline assessments (SCREENING) **(RANDOMISATION)**	Visit 1: i) Auxological a. Height b. Weight c. BMI d. Date of Birth e. Gender ii) Diabetes clinical a. Date of diagnosis b. Fasting C-peptide with paired glucose c. HbA1c d. Seated blood pressure (average of 2 readings) e. Total daily dose of insulin (mean of previous 7 days), basal and bolus proportion, carbohydrate ratio and insulin sensitivity factor f. History of hypoglycaemic events in past 12 months g. History of diabetes ketoacidosis in past 12 months h. Co-morbidities and medications iii) Psychology measures (baseline, age specific) Visit 6: i) CGM glycaemic data ii) Loss of work (participant/parent) or school iii) Biomarkers iv) Total daily dose of insulin (mean of previous 7 days), basal and bolus proportion, carbohydrate ratio and insulin sensitivity factor
Midpoint assessments	Visit 11: i) HbA1c ii) 2 weeks blinded CGM data, and all secondary glycaemic measures iii) Treatment satisfaction iv) Psychology measures v) Total daily dose of insulin (mean of previous 7 days), basal and bolus proportion, carbohydrate ratio and insulin sensitivity factor vi) Auxology (height, weight) vii) Seated blood pressure (average of 2 readings)
End of study assessments	Visit 16: i) Auxological a. Height b. Weight ii) CGM glycaemic data and all secondary glycaemic measures

	iii) Seated blood pressure (average of 2 readings) iv) Total daily dose, basal and bolus proportion, carbohydrate ratio and insulin sensitivity factor v) Psychological assessments (age specific) vi) Biomarkers vii) Semi structured interview
Continuous Assessments	i. Technology interactions/human factors (repeated sampling through mobile phone app. ii. Investigator time spent training (carbohydrate counting, HCL training) and support. iii. Time off work and school iv. Consumable use (sensors, pump sites) v. Health care providers expectations and experiences (repeated sampling through mobile phone app)
Procedures for safety monitoring during trial	Safety measures will be recorded including ketone levels. Establishment of a data safety and monitoring board (DSMB) to scrutinise conduct of the study and study team and to monitor safety data arising from the study in order to determine if stopping the trial is required. Refer appendix 15.12
Criteria for withdrawal of participants on safety grounds	A subject may terminate participation in the study at any time without necessarily giving a reason and without any personal disadvantage. An investigator can stop the participation of a subject after consideration of the benefit/risk ratio. Possible reasons are: 1. Serious Adverse Events 2. Inability to meet study requirements (e.g. regularly upload pump history to computer) 3. Technical grounds 4. Early termination of the study at the request of the steering committee or data safety monitoring board

2. Study flow


Study Design for Multi-Centre RCT, HCL Vs Standard Therapy:
Visit 1
Visit 2*
Visit 3-5
Visit 6
Visit 7*
Visit 8
Visit 9-10
Visit 11
Visit 12-15
Visit 16
Standard Therapy: 26 weeks
n= 80 (40CSII, 40 MDI)
END
Study Start
5+ Weeks Duration
Hybrid Closed Loop: 26 weeks
n=80
END
Eligibility Check
Run in, CGM and Carb counting
RANDOMIZE
• HbA1c ≤10.5%
• MDI or CSII
• 12 – 25yrs
• C-peptide <0.1nmol/L
• Provide information
• Consent
• Visit 2* First 2 weeks CHO counting for MDI subjects, and refreshers offered for CSII.
• Visit 3-5**: Blinded CGM insertion and training, 3 weeks CGM collection.
*Additional visits as required until carbohydrate counting competency
** Weekly contact to change and upload blinded CGM required
• Visit 6: Check for ≥ 70% CGM data to be eligible for randomisation
• Randomize, stratified by time in target glycaemic range (3.9-10mmol/L), age, diabetes duration and study site.
*MDI → HCL:
Visit 7A: Pump training and pump start.
Visit 7B (+3 days): Line change and review
Visit 7C (+14 days): CGM training
Visit 7D (+14 – 28 days): Start HCL
CSII → HCL
Visit 7A: Pump training, CGM training and pump start.
Visit 7B (+3 -7 days): Start HCL
Visit 8 (+4 weeks): Face to face review
Visit 9-10 (+11 weeks): Blinded CGM start
** Weekly contact to change and upload blinded CGM required
Visit 11 (+13 weeks): Midpoint measures
Visit 12-15 (+23 weeks): Blinded CGM start
** Weekly contact to change and upload blinded CGM required
Visit 16 (+26 weeks): Endpoint measures
Midpoint Measures
Baseline Measures
Continuous measures
Endpoint Measures

3. Introduction

There are over 120,000 people in Australia with Type 1 diabetes (T1D) (1). Approximately 10,000 of these are children and the incidence is increasing by around 3.5% each year (1). Despite modern treatment, complications of T1D and a reduced life expectancy continue to be a reality for patients. Attempts to aggressively manage blood glucose levels in order to avoid long-term complications are limited by difficulty, the risk of hypoglycaemia and the burden of care involved. Severe hypoglycaemia is associated with significant morbidity and even mortality and creates a fear of hypoglycaemia and anxiety for patients and their caregivers, affecting quality of life, and promoting behaviours aimed at avoiding hypoglycaemia (2). These actions lead to hyperglycaemia, placing patients at higher risk of developing long term complications. Fewer than a third of young patients in Australia reach a HbA1c of less than 7.5%, a target which has been shown to significantly reduce the development of complications associated with T1D (3, 4).

Approximately one third of patients with T1D have impaired hypoglycaemia awareness(5-8), and have an associated threefold increase in the likelihood of having a severe hypoglycaemic event(8). For the patient, repeated severe hypoglycaemic events have long lasting consequences which impact upon quality of life and daily activities such as driving. This results in increased anxiety and a greater burden on caregivers. The average cost of a severe hypoglycaemic event managed by the Australian health system is $2430.65 (9), and this does not take into account costs incurred by the community due to time off work (caregivers and patients).

T1D diabetes affects cognitive function, social function, and places a large health and economic burden on families and the community(1). In 2008-2009, $214 million of healthcare expenditure was for Type 1 diabetes (10). Patients with poor glycaemic control are likely to disproportionally contribute to healthcare costs. For all these reasons, it is essential to develop new therapies.

Almost universally, patients with T1D suffer from both hypoglycaemia and hyperglycaemia: this impacts their physical health, as well as their psychosocial wellbeing and places significant burden on communities including caregivers, families, workplace, and health service providers. The potential benefit of closed loop technology is to improve glycaemic control, while simultaneously reducing the burden of care for patients and carers, and improving psychosocial wellbeing. Hence, it is urgent that new innovations are made available to patients with T1D, and translated into routine clinical practice.

4. Names and intended use of devices

4.1 Hybrid Closed Loop System:

The intervention arm will use the MiniMed^{TM} 670G insulin pump, coupled with a 4th generation glucose sensor and GST3C transmitter. The closed loop algorithm is contained in the MiniMed^{TM} 670G insulin pump, using a modified proportional integrative derivative (PID) model, with insulin feedback and additional safety features. The algorithm receives CGM data every 5 minutes, and a "basal rate" insulin delivery is computed and adjusted every five minutes. Therefore, standard "basal" insulin that is pre-programmed in regular insulin pump therapy is replaced by the algorithm derived insulin delivery (given as a micro-bolus every 5 minutes). Meals will still be announced, and an insulin bolus delivered according to the

individualised patient carbohydrate ratio and insulin sensitivity factor (should a correction bolus be required in addition to the insulin for carbohydrate).

4.2 Blinded CGM

Blinded CGM will be collected three times during the study (baseline – at visit 3 for three weeks, midpoint – prior to visit 11 for two weeks, and prior to end for 3 weeks). A 4th generation sensor will be inserted and a GST3C connected. If there is any technical reason for the CGM data not being available for the minimum amount, participants will be offered additional CGM collection to meet the requirements of the protocol. Participants will be required to record finger prick glucose levels at least twice a day. CGM data is collected by uploading the GST3C and finger prick values from the CONTOUR® NEXT LINK 2.4 from Bayer.

4.3 Glucose monitoring

All participants will be issued with the CONTOUR® NEXT LINK 2.4 from Bayer. This glucose monitor requires CONTOUR PLUS test strips. For participants randomized to HCL, this allows for data to be directly sent to the insulin pump. For participants not on HCL, the CONTOUR® NEXT LINK 2.4 will be used in addition to their regular meter during CGM collection.

4.4 Carelink Software

Carelink is a Medtronic web based platform which is used for uploading insulin pump data. The Medtronic 670G can be uploaded, using the CONTOUR® NEXT LINK 2.4, which is plugged into the USB port of a PC. The software is Apple and Windows compatible. Insulin pump data is then accessible for download by the investigators.

5. Hypothesis of the randomized controlled trial

HCL will increase time in sensor glucose target range (3.9 – 10mmol/L) compared to standard therapy (CSII and MDI) by 10% (11). HCL will also reduce time spent hypoglycaemic by 60% (<3.9mmol/L).

6. Study rationale, objectives and endpoints

6.1 Study rationale

Hybrid closed-loop insulin delivery, with automatic glucose sensing and insulin delivery reducing patient intervention, offers the potential to circumvent the significant glycaemic excursions associated with conventional therapy. Superior glucose control has been demonstrated along with lower rates of hypoglycaemia in many in-clinic studies, diabetes camp studies, hotel studies (12), and now in the first emerging short term outpatient studies (13-15) (including our pilot data). As such, closed-loop insulin delivery looks able to revolutionize T1D therapy. In hybrid closed loop systems, meals are still announced and bolus insulin is delivery according to the patient's individualised carbohydrate ratio, and insulin sensitivity.
We have recently conducted pilot studies using the Medtronic hybrid closed loop system and initial home studies have shown promise of its potential for more prolonged controlled trials (16).
The primary rationale is to quantify glycaemia with the use of the HCL system versus standard therapy (either MDI or CSII), including time in target range, as well as glycaemic excursions either hypoglycaemia or hyperglycaemia. We will explore the impact of this system on fear of hypoglycaemia and quality of life and other psychological measures. We seek to quantify the economic impact of HCL compared to standard therapy for translational purposes.

Vascular complications are a major cause of morbidity and premature mortality in people with diabetes, contributed to by a mix of traditional and novel vascular disease risk factors. Traditional risk factors include adiposity, dyslipidaemia, hypertension, smoking and poor glycaemic control. Novel vascular disease risk factors include subtle changes in lipoproteins, such as oxidation and non-enzymatic glycation, Advanced Glycation End Products (AGEs), oxidative stress, inflammation, altered angiogenesis, prothrombotic tendencies, glycaemic variability, impaired vasoregulation, and more recently recognised molecular changes. Molecular changes include telomere length, activity of telomerase (the enzyme which controls telomere length), microRNAs and DNA methylation.
Collection of suitable samples and their analyses are particularly relevant to this study as vascular damage starts early in life, particularly in people with Type 1 diabetes, better metabolic control may at least partially reduce adverse risk factor profiles and as yet unexplained residual risk remains in people with diabetes even when all traditional risk factors are controlled. Furthermore, we have cross-sectional data demonstrating improved vascular function and a less adverse novel vascular risk profile in insulin pump treated Type 1 diabetic patients and evidence that molecular markers can be improved by existent and emerging drug therapies.

This study will be conducted in 5 tertiary paediatric diabetes centres in Australia. They are Perth Children's Hospital, Perth; The Children's Hospital at Westmead, Sydney; John Hunter Children's Hospital, Newcastle; Royal Children's Hospital, Melbourne; and Women's and Children's Hospital, Adelaide. A home visit may be offered for some visits which involve insertion of blinded sensors prior to randomisation, mid and end of the study. This provides a patient centric approach working within the parameters of local policies and procedures on home visits. A All sites have a large cohort of patients with T1DM with a significant proportion of insulin pump usage, and have recent experience with a multi-centre clinical trial. This will support recruitment targets, allowing timely progression through the study. Also we may use advertisements, notices, and/or media to

recruit subjects. Examples include flyers posted in public settings, newspaper ads, and radio and television advertisement. All advertisements and recruitment materials (e.g., video, audio, and telephone scripts) will be submitted to HREC for prior approval.

6.2 Study Objectives

6.2.1 Primary Objective:

The primary objective is to compare the proportion of time spent in target glycaemic range (sensor glucose level 3.9 - 10 mmol/l) while using HCL or using standard therapy (MDI and CSII).

6.2.2 Secondary Objectives:

The secondary objectives are to compare the efficacy of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System versus standard therapy (MDI and CSII) by the measurement of the following:

1.Glycaemic(24hr, day (0600 – 2400), night (0000 – 0600))

CGM data will be collected in three time blocks; baseline (3 weeks CGM), 13 weeks (2 weeks CGM) and 26 weeks (3 weeks CGM) post randomisation. A sub analysis of HCL vs. MDI and HCL vs. CSII is planned.

i. CGM data:
    a. % CGM Time <2.8 mmol/L
    b. % CGM Time <3.3 mmol/L
    c. % CGM Time <3.9 mmol/L
    d. % CGM Time 3.9-7.8 mmol/L
    e. % CGM Time >10.0 mmol/L
    f. % CGM Time >13.9 mmol/L
    g. % CGM Time >16.7 mmol/L
    h. Standard Deviation and Coefficient of Variation of CGM values
    i. Mean CGM glucose
ii. Average Fasting blood glucose (mmol/L), as measured during the three CGM time blocks at baseline, 13 weeks and 26 weeks. Defined as fasting capillary blood glucose level on waking (between 5am and 9am), at least 6 hrs after an insulin bolus for carbohydrate.
iii. Average Glycaemic control as measured by HbA1c collected at baseline, 13 weeks and 26 weeks post randomisation.
iv. Hospitalisations rate for diabetic ketoacidosis over the 7 month study period.
v. Episodes of severe hypoglycaemia over the 7 month study period (defined having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or i.v.glucose).

2. *Clinical measures*

The compare the difference between HCL insulin delivery vs standard therapy for the following measures

i) Change in auxological parameters (height, weight,BMI)
ii) Change in total daily dose , including basal and bolus proportion, carbohydrate ratios and insulin sensitivity

3. Psychosocial:
Questionnaires will be conducted on 3 occasions: at baseline , 13 weeks and 26 weeks.

i. **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*
ii. **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*
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To assess participant technology interaction and explore adherence patterns and approaches that may improve it. Repeated sampling methodology will be used. A series of questions will be asked once a week via a phone app, which will take less than 1 minute to complete.

5. Health-economic

To assess the health economic impact of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System vs standard therapy (MDI and CSII). The following data points will be used as part of the economic analysis:

i. QALYs calculated from the EQ-5D
ii. Hypoglycaemic events and HbA1c
iii. Participant reporting on work interruption
iv. Investigator reporting time spent on training, education and support, by the type of health professional resource used
v. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin).

*6. Biomarkers (*all ages)

To assess the impact of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System Vs standard therapy (MDI and CSII) on the biomarkers listed below. Biomarkers will be tested from blood and urine samples at baseline, and 26 weeks post randomisation.

i. Cell Adhesion Molecules (CAM)S
ii. Soluble vascular cell adhesion molecules sVCAM

iii. Soluble intercellular adhesion molecules sICAM
iv. s-e Selectin
v. Oxidized Low density lipoprotein
vi. Myeloperoxidase.
vii. MicroRNA signatures for arterial, renal and retinal complications
viii. Telomerase
ix. DNA methylation/acetylation
x. Glycomark
xi. Isoprostanes and proteomics
xii. Clotting profile

7. Performance Parameters

To assess the performance of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System, and components. The following measures will be used:

i. Proportion of time hybrid closed loop is active
ii. Unplanned exits from closed loop (*n*)
iii. Sensor performance – mean absolute relative difference (MARD), sensor failures (*n*)
iv. Insulin delivery line performance – reported delivery line failures (*n*)

8. Health Care Professionals Experiences and Expectations

To assess the health care professional's experiences and expectations of hybrid closed loop technology throughout the study.

6.3 Study Endpoints

6.3.1 Primary Endpoint:

The % time sensor glucose level is in target range (3.9–10 mmol/L) during HCL insulin delivery vs standard therapy (MDI and CSII), measured 23-26 weeks post-randomisation.

Secondary Endpoints:

1. Glycaemic:

Assess the average difference between standard therapy (MDI and CSII) in the following measures:

i. CGM data:

a. % CGM Time <2.8 mmol/L
b. % CGM Time <3.3 mmol/L
c. % CGM Time <3.9 mmol/L
d. % CGM Time 3.9-7.8 mmol/L
e. % CGM Time >10.0 mmol/L
f. % CGM Time >13.9 mmol/L

g. % CGM Time >16.7 mmol/L
h. Standard Deviation and Coefficient of Variation of CGM values
i. Mean CGM glucose

ii. Average Fasting blood glucose (mmol/L), as measured during the CGM time blocks at baseline, 13 weeks and 26 weeks post randomisation. Defined as fasting capillary blood glucose level on waking (between 5am and 9am), at least 6 hrs after an insulin bolus for carbohydrate.
iii. Average Glycaemic control as measured by HbA1c collected at baseline, 13 weeks and 26 weeks post randomisation.
iv. Hospitalisations rate for diabetic ketoacidosis over the 7 month study period.
v. Events of severe hypoglycaemia over the 7 month study period.

A sub- analysis of HCL vs. MDI and HCL vs. CSII is planned.

NOTE: Ketone measurement is not an outcome measurement in this trial, and all participants will be instructed to measure their ketones as per their routine clinical care.

2. Clinical:

The difference between HCL insulin delivery vs standard therapy for the following measures

i) Auxological parameters (height, weight,BMI)
ii) Insulin delivery: total daily dose , including basal and bolus proportion, carbohydrate ratios and insulin sensitivity

3. Psychosocial:

Assess the average difference between standard therapy (MDI and CSII) in the following measures:

i. **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*
ii. **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*
iii. **Anxiety***: State-Trait Anxiety Inventory (Child version for 12-15yrs, adult version ≥16-<25yrs)*
iv. **Impact and Satisfaction***: The Diabetes Treatment Satisfaction Questionnaire status and change version (16 - <25years)*
v. **Quality of Life***:12-<25years: EQ-5D-Y,*
vi. **Diabetes specific quality of life***: PedsQL – Child version (12years) Adolescent version (13 – 18 years) and young adult version (18 – <25 years).*
vii. **Diabetes distress:** *Problem Areas in Diabetes (Teen version for 12 – 17 years, standard version ≥17-<25yr)*
viii. **Participant reported outcome for Automated Delivery system:** *INSPIRE Questionnaires : baseline and post-assessment versions Child version (12 year olds), Adolescent version (13-18) and adult version(18-25)*
ix. **Semi structure interview** (all ages – post study, PCH only)

4. Human-technology interaction:

Describe participant technology interaction, adherence patterns and approaches that may improve it.

5. Health-economic

The health economic impact of HCL insulin delivery vs standard therapy using data derived from:

i. QALYs calculated from the EQ-5D
ii. Hypoglycaemic events and HbA1c
iii. Participant reporting on work interruption
iv. Investigator reporting time spent on training, education and support, by the type of health professional resource used
v. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin).

6. Biomarkers (all ages)

Assess the difference between MiniMed™ 670G Insulin Pump Hybrid Closed Loop System vs standard therapy (MDI and CSII) after 6 months of treatment on the following biomarkers:

i. Cell Adhesion Molecules (CAM)S
ii. Soluble vascular cell adhesion molecules sVCAM
iii. Soluble intercellular adhesion molecules sICAM
iv. s-e Selectin
v. Oxidized Low density lipoprotein
vi. Myeloperoxidase.
vii. MicroRNA signatures for arterial, renal and retinal complications
viii. Telomerase
ix. DNA methylation/acetylation
x. Glycomark
xi. Isoprostanes and proteomics
xii. Clotting profile

7. Performance Parameters

To report the performance of the MiniMed™ 670G Insulin Pump Hybrid Closed Loop System, and components. The following measures will be used:

i. Proportion of time hybrid closed loop is active
ii. Unplanned exits from closed loop (*n*)
iii. Sensor performance – mean absolute relative difference [MARD], sensor failures (*n*)
iv. Insulin delivery line performance – reported delivery line failures (*n*)

8. Health Care Professional Experiences and Expectations
To report health care provider's experiences and expectations of hybrid closed loop systems through the study duration

7 Design of the randomized controlled trial

7.1 Statement of design and randomisation

This is a prospective, randomized multi-centre study in adult and paediatric subjects from Australia, with type 1 diabetes mellitus aged 12 – 25 years. Participants can be on CSII or MDI treatment regimens to be eligible. After a run-in phase, subjects will be randomly assigned to one of the following two arms:

HCL arm: MiniMed^{TM} 670G for 6 months; OR
Conventional arm: MDI or CSII for 6 months.

Randomization will be stratified based on 4 variables: Time spent in target sensor glucose range (3.9 – 10mmol/L) – with participants evenly split above and below 55%(17) time in target range, age, diabetes duration, and centre site. This will be managed by the Clinical Trials Centre in Sydney.

7.2 Sample size determination and power calculations

Study Subjects:
Children, adolescents and adults with T1DM aged between 12 and less 25 years with diabetes duration of at least 1year and c-peptide <0.1nmol/L, HbA1c <10.5% and on insulin pump therapy for at least 3 months OR multi-daily injections (≥4 per day) will be eligible for the trial. Inclusion and exclusion criteria are expanded upon below.

Sample size:

Sample size is computed for a parallel design RCT with 2 groups comparing a hybrid closed-loop system with usual care in individuals with type 1 diabetes with HbA1c <10.5%; with time in range 3.9 – 10mmol/L at 6 months as primary outcome. Sample size is computed for a paediatric study age 12-<25 years old.
To estimate the total sample size, data from the JDRF CGM RCT were used(17). There were N=97 12-<25 years of age, who used injections or pumps at enrolment, had a baseline HbA1c value <10.5%, were randomized to the control group (usual care), and had blinded CGM data at randomization and at 6 months. The confidence interval for the effective SD (after adjusting for baseline) was 15% for the younger group.
Assuming parallel groups, normal distribution for the treatment effect, a 1:1 allocation, a 2-tailed test with null hypothesis stating that the difference is zero, no corrections for multiple comparisons, and a type I error = 5%, the following total sample size is required:

- To detect a 10% difference, using an SD of 13%, and 85% power, 64 subjects are required in each arm. Allowing for 20% predicted drop-out, **80 subjects** will be enrolled to each arm **(160 total participants).**

This study is also powered to detect a difference in time spent in the hypoglycaemic range (<3.9mmol/L) using the same JDRF CGM RCT data. Since time below 3.9mmol/L at 6 months

is not normally distributed, its mean was estimated using a robust procedure. On the other hand, since differences in time below 3.9mmol/L from randomization to 6 months are normally distributed, the SD and the effective SD were estimated using the raw/untransformed data.
The two point estimate and 95% CI confidence intervals for the effective SD 6% (95% CI: 5% to 7%). The estimated robust (MM estimate that down-weights outliers means for % time below 3.9mmol/L at 6 months is 5.7%.
The required total sample size (assuming parallel groups, normal distribution for the change in treatment effect, a 1:1 allocation, a 2-tailed test with null hypothesis stating that the difference is zero, no corrections for multiple comparisons, and a type I error = 5%) is:

- 12-<25 years: **100 participants** required to detect a 60% reduction in time spent <3.9mmol/L (using a 6%SD and 80% power). This is less than the 160 recruitment target to demonstrate an improved time spent in range.

7.3 Statistical Analysis

All statistical analyses will be performed using SAS for Windows (SAS Institute Inc) and STATA (StataCorp). The analysis population will be the intention-to-treat population, which will be defined as all participants who are randomised and have at least 1 visit after baseline. P-values <.05 will be considered statistically significant and 2-sided P-values will be reported. Descriptive statistics will be used to characterize participants at study entry

Primary endpoint
The primary endpoint, average % time spent in target glycaemic range (sensor glucose level 3.9 - 10 mmol/l) during 6 months, will be analysed using Analysis of covariance (ANCOVA) adjusting for baseline percentage score and site. Least square means and least square mean differences and their associated 95% confidence intervals will be presented for each treatment group and between groups. In the event that data are not normally distributed the Mann–Whitney–Wilcoxon (Wilcoxon Rank-Sum) Test will be employed which tests the medians. In addition if data are skewed, bootstrap methods(21) will be used which allows for a non-parametric test of the arithmetic means. Bootstrap methods simply estimate the distribution of the statistic through resampling with replacement (many times) from the original data population. These methods will also be employed for average % CGM as outlined in the secondary objectives.

Sensitivity analysis
The primary endpoint analysis will be re-run with the PP population as a sensitivity analysis.
Secondary endpoints.
Coefficient of variation will be reported for each group: bootstrap methods will be used to estimate variability as appropriate.

Rates of hospitalisations for severe hypoglycaemia and moderate hypoglycaemia as per participant log will be analysed as unadjusted incidence rates based on the Poisson distribution. Incidence rates and incidence rate differences will be presented with their associated 95%confidence intervals calculated as exact Poisson confidence limits(22). In addition, where

appropriate Poisson or negative binomial regression models will be fitted e.g. moderate hypoglycaemia events from the participant log. If there are a high proportion of zero counts, zero inflated Poisson (ZIP) or zero inflated negative binomial models (ZINB) will be considered. If counts are sparse then rates will be reported descriptively only. Number of hospitalisations due to diabetic ketoacidosis events and other safety outcomes will be tabulated and presented as n and %.

Continuous outcome measures (including psychosocial) collected at baseline and endpoint will be analysed using ANCOVA adjusting for baseline score and site. Measures collected at baseline, 3 months and endpoint (e.g. *HbA1c, Fasting capillary blood glucose , Mean CGM glucose, Hypoglycaemic Fear Survey-II Worry scale, Child State-Trait Anxiety Inventory, The Diabetes Treatment Satisfaction Questionnaire status and change version , Problem Areas in Diabetes, Impaired awareness of hypoglycaemia: GOLD SCORE, INSPIRE questionnaires*) will be analysed using mixed models repeated measures (MMRM) adjusting for baseline score (where appropriate), group, period (baseline, 3 months, 6 months) and site. A random intercept term for 'individual' will also be employed if deemed appropriate. Least square means and least square mean differences and their associated 95% confidence intervals will be presented for each group and between groups. Unstructured covariance matrix will be used unless other covariance structures are more appropriate as determined by the Bayesian information criteria (BIC). Human technology interaction and health care professional experiences and expectations analyses will be reported Exploratory; descriptive analysis.

A separate economic analysis will be conducted. Using measures (e.g. QALYs calculated from the EQ-5D) collected during the trial.

Performance Parameters will be reported descriptively (n, % for categorical measures and n, mean, median, standard deviation, minimum and maximum for continuous measures)

Subgroup and exploratory analysis

Subgroup analysis will be performed to examine differences in treatment effect based on participant characteristics. Subgroup analysis will be treated as exploratory, with the intent of hypothesis generation. A treatment by subgroup interaction term will be included in the MMRM to assess differential effects by subgroup. Subgroup analyses may include (but not be limited to):

- Age
  - <12 years
  - >12 years
- BMI category
  - <18
  - 18 – 25
  - > 25
- Diabetes duration
  - <6 years
  - 6 years or longer
- HbA1c at baseline.
  - <8%
  - 8% or greater

A range of additional exploratory analyses will be conducted. These analyses may include (but not be limited to):

- Differential effects of intervention based on time of day
- Examination of time spent in various glycaemic ranges
- Finer-grained analysis of BGL patterns
- Relationship between CGM usage/adherence and outcomes
- Differences in effect size based on control treatment regimen

Techniques used for subgroup and exploratory analysis will depend upon the distribution of the outcome measure and will include presentation/comparison of unadjusted rates with Poisson confidences limits (or negative binomial models where overdispersion is indicated), measures of central tendency and dispersion, mixed modelling, analysis of covariance, and novel graphical presentation.

7.4 Inclusion and exclusion criteria

7.4.1. Inclusion criteria:

1. Type 1 diabetes (diagnosis consistent with American Diabetes Association Classification of Diabetes Mellitus) diagnosed at least 1 year ago
2. Fasting C-peptide <0.1 nmol/L (in the absence of hypoglycaemia) within the last 3 months
3. Insulin regimen either:
   - Multiple daily injections (MDI) with ≥4 injections per day (≥3 rapid-acting insulin and ≥1 long-acting insulin); or
   - Insulin pump therapy (CSII) established for ≥3 months
4. Aged 12-<25years
5. HbA1c ≤10.5%
6. Living in an area with internet and cellular phone coverage
7. English speaking

7.4.2 Exclusion Criteria

A subject is excluded from the study if any of the following criteria are met:

1. Chronic kidney disease (eGFR <45mL/min/1.73m^2)
2. Use of any non-insulin glucose-lowering agent within the past 3 months
3. Oral or injected steroid use within the past 3 months
4. Pregnancy, or planned pregnancy within study period
5. Uncontrolled coeliac disease (not following a gluten free diet), or other untreated malabsorption
6. Uncontrolled thyroid disease
7. Clinically-significant gastroparesis
8. Uncontrolled hypertension (DBP >100 mmHg and/or SBP >160 mmHg)
9. History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack (TIA), stroke, or thromboembolic disease in the past 3 months.
10. Poor visual acuity precluding use of the investigational technology
11. Inability or unwillingness to meet protocol requirements (including carbohydrate-counting, CGM use as per allocated study group only).
12. Severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements

Visit Schedule	Pre screening																	
CRF visit number		1	2ǂ	3	4	5	6*	7*ǂ	8	9	10	11	12	13	14	15	15a#	16ϕ
Length of time of visit (hours)		4	2 to 8	2	1.5	1.5	4	0.5 to 8	1	1.5	1.5	4	1.5	1.5	1.5	4	1.5	4
Weeks from Randomisation (+/- 2 week window either side of visit)		-4ϒ	-3ϒ	-3	-2	-1	0	0	4	11	12	13	23	24	25	26	26+1	26
Informed Consent		x																
Auxological data		x					x					x						x
Diabetes clinical history		x																
C-peptide	x (local)						x											
U + Es	x																	
bHCG		x																
HbA1c	x						x					x						x
Blood pressure		x					x					x						x
Total Daily Dose		x					x					x						x
Carbohydrate Counting			x															
Insulin pump review			x						x			x						
Pump training								x										
Logbook data recorded				x	x	x		x	x	x	x	x	x	x	x	x	x	x
logbook data collected							x					x				x	x	
CGM				x	x	x				x	x		x	x	x	+/-x	x	
Psychology measures		x					x					x				x		
Modified momentary Sampling								x	x	x	x	x	x	x	x	x	x	
Biomarkers							x											x
Semi-structured Interview																		x

ϒ Length to randomisation may vary according to education level

ǂ Length of time and number of visits (2a, 2b…) will depend on baseline management regimen and carbohydrate counting knowledge

* Variation in requirement depending on randomisation

ϕ Random selection of participants will be offered semi-structured interview

\# only needed if insufficient CGM

7.4 Visit schedule

Pre-screening of HbA1c, eGFR and C-Peptide for eligibility will be required, to occur within 3 months of formal screening.

VISIT 1 4hr. (Screening and Eligibility Check).

Information sheets will be provided in advance to participants who potentially fit inclusion criteria. Participants will be checked if they meet the inclusion criteria listed above. All post menarche females will have a βHCG test to exclude pregnancy. The following data will be recorded:

1. Consent signed by participant and investigator
2. Demographic
    a. Date of Birth
    b. Gender
3. Auxological
    a. Height
    b. Weight
    c. BMI
4. Diabetes clinical
    a. Date of diagnosis
    b. C-peptide (local laboratory value can be used for the purpose of the 0.1nmol/L cut off within 3 month of screening visit, and formal samples will be stored for centralised assay at a later date).
    c. HbA1c (local laboratory or DCA value can be used for the purpose of the 10.5% cut off)
    d. βHCG for all post menarche females
    e. History of severe hypoglycaemia – coma or convulsion or requiring help from others (events in last 12 months).
    f. Seated blood pressure (average of 2 readings)
    g. Total daily dose of insulin (mean of previous 7 days)
    h. Carbohydrate ratios and insulin sensitivity factors
    i. Co-morbidities and medications
    j. Smoking and alcohol intake
5. Psychology measures:

    Psychological scales will be on an electronic platform where applicable.

    a) **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*
    b) **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*
    c) **Anxiety***: State-Trait Anxiety Inventory (Child version for 12-15yrs, adult version ≥16-<25yrs)*
    d) **Impact and Satisfaction***: The Diabetes Treatment Satisfaction Questionnaire status and change version (16 - <25years)*
    e) **Quality of Life***:12-<25years: EQ-5D-Y,*
    f) **Diabetes specific quality of life***: PedsQL – Adolescent version (13 – 18) and young adult version (18 – <25).*
    g) **Diabetes distress:** *Problem Areas in Diabetes (Teen version for 12 – 17 years, standard version ≥17-<25yrs)*
    h) **Participant reported outcome for Automated Delivery system:** *INSPIRE Questionnaires : baseline and post-assessment versions Child version (12 year olds), Adolescent version (13-18) and adult version(18-25)*

VISIT 2* (within 4 weeks of Visit 1 run in and education planning)

An individual education program will be planned to occur over the next 2 weeks, and will vary according to the prior knowledge and baseline treatment of that participant.

i. CSII as baseline treatment
   a) Carbohydrate Counting: 1 x dietician review (1 -2 hours)
   b) General pump review: 1 x diabetes educator session (1 – 4 hours) to review pump settings, download capability.

ii. MDI as baseline treatment
   a) Carbohydrate Counting: 1 – 3 x dietician (1 -2 hours) review over a week period (prior to visit 3). This may be extended over a period of 3 weeks if deemed clinically necessary. Participants will be issued with an Aviva Expert (Roche) glucometer and testing strips, which will be programmed with individual carbohydrate ratio, and insulin sensitivity.

VISIT 3 (1.5 hrs)

This visit starts the official glycaemic baseline data collection point. This constitutes 21 days of blinded continuous glucose monitoring. The study participant will attend the research facility to have a 4th generation sensor inserted and GST3C minilink attached. Subjects will receive the following instruction:

i. Expectations of minimum 4x/day glucose testing using CONTOUR® NEXT LINK 2.4 glucometer. Participants will be instructed that an addition to any glucose values recorded on their usual glucometer, they will need 4x additional values (can be taken concurrently) taken on a CONTOUR® NEXT LINK 2.4 glucometer which will be issued to them at this visit.
ii. Instructed to collect prospective data over the following 21-28 days and record into the diary:
   1. Symptomatic hypoglycaemia requiring carbohydrate rescue
   2. Time off work / school (including parents)
   3. Insulin dosing (MDI participants)
iii. Instruction on the logbook, with respect to identifying contacts (investigative staff) for trouble shooting and technical issues for the following 21-28 days.

At this visit, all participants will be issued with the following:

i. Participant logbook
ii. CONTOUR® NEXT LINK 2.4 glucometer

VISIT 4 and Visit 5 (30 minutes each)

7 days after sensor insertion, participants will return to download the first week of CGM data. The CONTOUR® NEXT LINK 2.4 glucometer will be uploaded. A new sensor will be inserted and a fresh GST3C attached. The logbook will be revised, and participants reminded to keep records accurate and up to date. This is repeated in another 7 days. If there is insufficient CGM data collected by visit 5 (>70% of of each 7 day period having CGM recordings),or due to a technical reason for the CGM data not being available for the minimum amount, participants will be offered additional CGM collection to meet the requirement of the protocol.

VISIT 6 (3 hours)

This visit is the randomization visit, and allocation is dependent on the stratifications listed previously.
The following data will be collected prior to randomization:

i. Auxological
   a) Height, weight, BMI.

ii. Diabetes clinical
   a) Blood pressure
   b) Previous 7 days' total daily dose insulin (including basal and bolus proportions)
   c) Carbohydrate ratios and insulin sensitivity factor
   d) Logbook will be collected. Symptomatic hypoglycaemia requiring carbohydrate rescue in the previous 14 days and time off work or school will be collected from the participant logbook

iii) Biomarkers

A detailed description of sample preparation for biomarkers is found in appendix 15.9. 12mL of blood and 50mL of urine will be collected.

a) Cell Adhesion Molecules (CAM)S
b) Soluble vascular cell adhesion molecules sVCAM
c) Soluble intercellular adhesion molecules sICAM
d) s-e Selectin
e) Oxidized Low density lipoprotein
f) Myeloperoxidase.
g) MicroRNA signatures for arterial, renal and retinal complications
h) Telomerase
i) DNA methylation/acetylation
j) Glycomark
k) Isoprostanes and proteomics
l) Clotting profile

Participant randomization will occur at the completion of the tasks above (for details on randomization process see section 7.3.1). Once randomized a date will be booked for entry into the study arm (visit 7), which should be no longer than 2 weeks after visit 6.

VISIT 7 (visit schedule dependent on randomization and baseline therapy)

i. THOSE RANDOMIZED TO **STANDARD THERAPY:**

MDI regimen: Participants will be issued a new logbook and instructed to prospectively to fill in interruptions from work/school.

CSII:. Participants will be issued a new logbook and instructed to prospectively to fill in interruptions from work/school and document any insulin pump technical issues (insulin infusion site failures).
Investigators will log all time spent training and communication with participant.

ii. THOSE RANDOMIZED TO **HCL THERAPY**:

MDI to HCL: Participants will require general pump education, and standard insulin pump therapy stabilization prior to HCL initiation.

Visit 7A: DNE initial pump training (8hours) including programming the pump, demonstrating line insertion

Participant will be issued the Minimed™ 670G insulin pump and participant user guide.

Visit 7B: Within the next three days, return to observe line change if required and participant is unconfident. Weekly phone/email contact to support pump transition for the following 2 weeks. Participants will upload their pump weekly. Communication can be more often – as per clinical need, and logged by investigators.

Visit 7C: 2 weeks after pump start: Initiate CGM (2 hours), with training on CGM use, alarm settings, training on CGM insertion and changing sensor. Initial low and high alarms will be set at 4.0mmol/L and 15mmol/L respectively, although these can be changed according to individual preference. Rate alarms, *suspend on low* and *suspend before low* functions **will not** be activated.

At this visit participants will be issued with 4th generation sensors and the GST3C transmitter, as well as CGM user guide and instructions for contact persons to assist any troubleshooting

Visit 7D: 2 – 4 weeks post pump start and stabilization, and a minimum of 3 days CGM, face to face for instruction on how to operate HCL, and HCL initiated (2 hours). There will be opportunity for those unfamiliar with CGM use to practice a sensor change with supervision. Upon HCL initiation, participants will be instructed to avoid excessive exercise for 48hrs while the algorithm adapts.

Further, at this point participants will be issued a new logbook and instructed to prospectively to fill in interruptions from work/school and document any insulin pump technical issues (insulin infusion site failures, sensor changes, unplanned exit from HCL). Participants will subsequently have weekly communication via phone call or email for support for the following 4 weeks, and upload their pump weekly. Investigators will log all time spent training and communication with participant. Communication can be more often – as per clinical need, and logged.

CSII to HCL: Participant 670G, CGM education and HCL training.

Visit 7A: Participants will be trained on how to use the Medtronic 670G insulin pump. They will also be instructed on how to link CGM on the Medtronic 670G pump (allow 2 -4 hours) and issued with Enlite III and the GST3C transmitter, as well as CGM user guide. Initial low and high alarms will be set at 4.0mmol/L and 15mmol/L respectively, although these can be changed according to individual preference. Rate alarms, *suspend on low* and *suspend before low* functions **will not** be activated.

Visit 7B: Once CGM data has been established for a minimum of 3 days, and maximum 7 days, participant returns for face to face instruction on HCL use and initiation. During this visit the sensor will be replaced, to demonstrate sensor warm up and HCL initiation, and provide an opportunity for those unfamiliar with CGM use to practice a sensor change with supervision. Upon HCL initiation, participants will be instructed to avoid excessive exercise for 48hrs while the algorithm adapts.

Further, at this point participants will be issued a new logbook and instructed to prospectively to fill in interruptions from work/school and document any insulin pump technical issues (insulin infusion site failures, sensor changes, unplanned exit from HCL). Participants will be issued glucose testing strips for the already issued CONTOUR® NEXT LINK 2.4 glucometer - enough to last 12 weeks.

Participants will subsequently have weekly communication via phone call or email for support for the following 4 weeks, and upload their pump weekly. Investigators will log all time spent training and communication with participant. Communication can be more often – as per clinical need, and logged.

VISIT 8: (4 weeks from Visit 7 if randomised to control))
(If randomized to HCL group, **4 weeks from Visit 7d)**

7.4.1 THOSE RANDOMIZED TO **STANDARD THERAPY**

Face to face meeting (1hr). Check logbook is being filled out. Revise CSII settings and MDI if necessary. If on CSII upload the insulin pump. Schedule visit 9 and 10.

7.4.2 THOSE RANDOMIZED TO **HCL**

Face to face meeting (1hr). Check logbook is being filled out. Upload insulin pump, and revise insulin sensitivity and carbohydrate ratio. Schedule visit 9.

VISIT 9 (11 weeks from Visit 7) 30 minutes)

i. THOSE RANDOMIZED TO **STANDARD THERAPY**

The study participant will attend the research facility to have a 4th generation sensor inserted andGST3C transmitter attached. Subjects will receive the following instruction:

a) Expectations of minimum 4x/day glucose testing using CONTOUR® NEXT LINK 2.4 glucometer.
b) Instructed to collect prospective data over the following 2 weeks and record into the logbook:
    1. Symptomatic hypoglycaemia requiring carbohydrate rescue
    2. Time off work / school
    3. Insulin dosing (MDI participants)

ii. THOSE RANDOMIZED TO **HCL**

Participants will have a 2nd, 4th generation sensor inserted andGST3C transmitter attached. Subjects will receive the following instruction:

a) Expectations of minimum 4x/day glucose testing using CONTOUR® NEXT LINK 2.4 glucometer.
b) Instructed to collect prospective data over the following 2 weeks and record into the logbook:
    1. Symptomatic hypoglycaemia requiring carbohydrate rescue
    2. Time off work / school

VISIT 10 (12 weeks from Visit 7), 30 minutes).

7 days after sensor insertion, participants will return to download the first week of CGM data. The CONTOUR® NEXT LINK 2.4 glucometer will be uploaded. A new sensor will be inserted and a fresh GST3C attached. The logbook will be revised, and participants reminded to keep records accurate and up to date.

VISIT 11: (13weeks since Visit 7), 4 hours).

All participants will have a clinical review of insulin settings (MDI, CSII and HCL) and refresher on carbohydrate counting. An additional CGM week and visit will be required if there is <70% of available CGM time available from the upload.

The following data will be collected at the midpoint:

i. Auxological
    a. Height, weight, BMI
ii. Glycaemic:
    a. CGM uploaded for standard therapy on MDI and CSII
    b. 670G uploaded for HCL participants
iii. Diabetes clinical
    a. HbA1c
    b. Blood pressure (average of 2 readings)
    c. Previous 7 days' total daily dose insulin (basal and bolus proportions for participants on insulin pump therapy)
    d. Carbohydrate ratios and insulin sensitivity
    e. Symptomatic hypoglycaemia requiring carbohydrate rescue in the previous 14 days from participant logbook.
iv. Psychological assessments:

a. **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*

b. **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*

c. **Anxiety***: State-Trait Anxiety Inventory (Child version for 12-15yrs, adult version ≥16-<25yrs).*

d. **Impact and Satisfaction***: The Diabetes Treatment Satisfaction Questionnaire status and change version (16 - <25years)*

e. **Quality of Life***:12-<25years: EQ-5D-Y,*

f. **Diabetes specific quality of life***: PedsQL – Child version (12 years), Adolescent version (13 – 18 years) and young adult version (18 – <25 years).*

g. **Diabetes distress:** *Problem Areas in Diabetes (Teen version for 12 – 17 years, standard version ≥17-<25yrs)*

Participants will be issued a third logbook for the second half of the study documenting symptomatic hypoglycaemia requiring carbohydrate rescue and interruptions from work/school, and document any insulin pump technical issues (insulin infusion site failures, sensor changes, unplanned exit from HCL).

Participants will be issued with enough consumables for the remainder of the study.

VISIT 12: week 23 from Visit 7. (30 minutes)

THOSE RANDOMIZED TO **STANDARD THERAPY**

The study participant will attend the research facility to have a 4th generation sensor inserted andGST3C transmitter attached. Subjects will receive the following instruction:

A) Expectations of minimum 4x/day glucose testing using CONTOUR® NEXT LINK 2.4 glucometer.

b) Instructed to collect prospective data over the following 3 weeks and record into the logbook:

1. Symptomatic hypoglycemia requiring carbohydrate rescue
2. Time off work / school
3. Insulin dosing (MDI participants)

iii. THOSE RANDOMIZED TO **HCL**

Participants will have a 4th generation sensor inserted andGST3C transmitter attached. Subjects will receive the following instruction:

a) Expectations of minimum 4x/day glucose testing using CONTOUR® NEXT LINK 2.4 glucometer.

b) Instructed to collect prospective data over the following 2 weeks and record into the logbook:

1. Symptomatic hypoglycaemia requiring carbohydrate rescue
2. Time off work / school

VISIT 13, 14 and 15 (24 and 25 and 26 weeks from Visit 7a, 30 minutes each). Note that visit 16 will occur on the same day as visit 15 if sufficient CGM data has been captured.

7 days after sensor insertion, participants will return to download the previous 7 days of CGM data. The CONTOUR® NEXT LINK 2.4 glucometer will be uploaded. A new sensor will be inserted and a fresh GST3C attached. The logbook will be revised, and participants reminded to keep records accurate and up to date. This is repeated for visit 13, 14 and 15 supplemental as required. If there is insufficient CGM data collected (>70% of of each 7 day period having CGM recordings),or due to a technical reason for the CGM data not being available for the minimum amount, participants will be offered additional CGM collection to meet the requirement of the protocol.

VISIT 16: Week 26 post randomization (**study end,** 4 hours)

The following data will be collected at the endpoint:

i. Auxological
   a. Height, weight, BMI.
ii. Glycaemic:
   a. CGM uploaded for those standard therapy (MDI and CSII)
   b. 670G uploaded for HCL participants
iii. Diabetes clinical
   a. HbA1c
   b. Blood pressure (average of 2 readings)
   c. Previous 7 days' total daily dose insulin (basal and bolus proportions for participants on insulin pump therapy)
   d. Carbohydrate ratios and insulin sensitivity
   e. Symptomatic hypoglycaemia requiring carbohydrate rescue in the previous 21 days from participant logbook.
iv. Psychological assessments:
   a. **Fear of hypoglycaemia***: Hypoglycaemic Fear Survey-II Worry scale: 17-<25years. Children's Hypoglycaemia Fear survey 12 – 17 years.*
   b. **Hypoglycaemia Awareness***: Hypoglycaemia Awareness Scale (Gold Score) (all ages)*
   c. **Anxiety***: State-Trait Anxiety Inventory (Child version for 12-15yrs, adult version ≥16-<25yrs).*
   d. **Impact and Satisfaction***: The Diabetes Treatment Satisfaction Questionnaire status and change version (16 - <25years)*
   e. **Quality of Life***:12-<25years: EQ-5D-Y,*
   f. **Diabetes specific quality of life***: PedsQL – Child version (12 years) Adolescent version (13 – 18 years) and young adult version (18 – <25 years).*

g. **Diabetes distress:** *Problem Areas in Diabetes (Teen version for 12 – 17 years, standard version ≥17-<25yrs,*
h. **Participant reported outcome for Automated Delivery system:** INSPIRE Questionnaires : baseline and post-assessment versions Child version (12 year olds), Adolescent version (13-18) and adult version(18-25)
i. **Semi structure interview** (all ages)

i. Biomarkers
12mL of blood and 50mL of urine will be collected.
a) Cell Adhesion Molecules (CAM)S
b) Soluble vascular cell adhesion molecules sVCAM
c) Soluble intercellular adhesion molecules sICAM
d) s-e Selectin
e) Oxidized Low density lipoprotein
f) Myeloperoxidase.
g) MicroRNA signatures for arterial, renal and retinal complications
h) Telomerase
i) DNA methylation/acetylation
j) Glycomark
k) Isoprostanes and proteomics
l) Clotting profile

Log books will be returned

A subset of participants will be take part in a semi-structured interview within 4 weeks of completing the study.

8 Study devices

The following devices will be used in the study: User guides are included in appendix 15.10

1. Minimed Medtronic 670G
2. CONTOUR LINK glucometer
3. 4th generation glucose sensors, and sensor inserter
4. GST3C CGM transmitter

9 Trial management

The day to day management of the study will be the responsibility of the Investigator at each centre. The Chief Investigator and Study Project Manager (PM) will maintain regular email correspondence with all investigators and study coordinators. The Chief Investigator, with the principal investigators will assume responsibility for the progress of the study in accordance with agreed timelines and milestones with the study funders. An independent Data Safety and Monitoring Board have also been established. The Study PM will liaise with the study teams in all centres to establish procedures and ensure that the study is carried out according to the protocol and to standards of GCP, with robust systems for reporting adverse events. The Data Manager will be responsible for the central preparations of data for presentation to the DSMB as requested.

Trial agreements have been established between all of the collaborating centres as well as with Medtronic for the provision of devices.

10 Data management

The Data Manager will be responsible for the central preparations of data for presentation to the DSMB as requested. At consent each subject will be given a unique identifying number based on their centre which will be used for data input to the centralized database. Study databases are developed "in house" and incorporate QC checks to ensure accurate data entry. Randomizations will be undertaken by the Investigators (or delegated person) in each centre. Pump information will be reviewed at each centre when uploaded by the participant, copied and de-identified. This de-identified copy with the participant's unique identifier code will be sent to the data manager in Perth.

11 Adverse Events and Safety Reporting

Each investigator has the responsibility to ensure arrangements are in place to record, notify, assess, report, analyse and manage adverse events in this study in order to comply with the Therapeutic Goods Administration (TGA) regulations and local Ethics requirements.

In addition, the following people at the lead site in Perth should be notified of all Serious Adverse Events immediately or within 24 hours of being made aware of the event to ensure appropriate notification to the DSMB.

Professor Timothy Jones Department of Endocrinology & Diabetes, Princess Margaret Hospital for Children, Roberts Road, Perth, WA, 6008 Tel: 08 9340 8090; Tim.Jones@health.wa.gov.au	Associate Professor Elizabeth Davis Department of Endocrinology & Diabetes, Princess Margaret Hospital for Children Roberts Road, Subiaco, Perth, WA 6008 Tel: 08 9340 8090 Elizabeth.Davis@health.wa.gov.au

Definitions:

Adverse Event Any undesirable clinical occurrence in a subject whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

Adverse Device Event
A clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of the device, or the performance of the device system.

Serious Adverse Event

A serious adverse event is to be reported within 24 hrs of notification that:

- Results in death
- Is life threatening
- Any in-patient hospitalisation or results in prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect

All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority (ies) and the IRB/IEC.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

The investigator must inform the HREC and the TGA (where appropriate) of all serious or unexpected adverse events that occur during the trial and may affect the conduct of the trial or the safety of the participants or their willingness to continue participation in the trial;
to inform the HREC as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the trial or which may indicate the need for amendments to the trial protocol.

The TGA require that all serious and unexpected adverse device events are reported to the Devices Clinical Section, Office of Blood, Devices and Tissues of the TGA in an expedited fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life-threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe. All other adverse device reactions and adverse events are tabulated as per usual trial protocols and produced on request.

11.1 Ethical considerations Informed Consent

All eligible subjects identified for the intervention study who wish to participate, will be asked to sign a consent form agreeing to the trial. The subjects recruited to the study who are under the age of consent will be able to provide informed consent and this will be obtained from their parents according to current ICH, Good Clinical Practice (GCP) and The National Statement on Ethical Conduct in Human Research 2007 (Updated May 2013). Children will not be able to give their legal consent but they will be asked to give assent and this will be appropriately documented. Both children and the parents will be provided with full information about the trial and adequate time to consider the risk/benefits of participation in the study. Subjects whose first language is not English will be provided with translated versions of information sheets and with interpreters to aid discussion before consent.

Consent will initially be obtained by the research nurse, who is not directly involved in routine clinical care of the participant and their families, to avoid any undue pressure to agree to participation. Written signed informed consent will be retained in the study site files. On achieving age of consent, the participants will be asked to sign forms agreeing to their continued involvement in the study. All participants will freely give their informed consent to participate in the study. A participant may decide to withdraw from the study at any time without prejudice to their future care.

Consent for health care professionals involved in the study to be surveyed during the trial using the mobile app will be implied by the willingness to complete the survey. A consent statement will be displayed before the user can proceed to the questions.

11.2 No fault liability

All of the investigators and research personnel will be indemnified for negligent harm based on local health service provision and personal investigators medical insurance provision.

11.3 Ethical committee review

The study protocol is to be seen and approved by the appropriate ethical review committees at all centres. Copies of the letters of approval will be filed in the study file.

11.4 National Statement/Declaration of Helsinki & ICH Good Clinical Practice

The study is to be carried out in conformation with the spirit and the letter of the Declaration of Helsinki, and in accord with the National Statement on Ethical Conduct in Human Research (2007) and ICH Good Clinical Practice Guidelines.

11.5 Sources of research material and confidentiality protections

All subjects will be allocated a unique Study Identification number and this will be used for the transfer of all data. Confidential data will be retained at the study sites in a secure study file. At all times the confidentiality of the subjects will be maintained, and reports to meetings and publications will not include confidential or data identifying individuals.

11.6 Changes to protocol

Any proposed protocol changes will be submitted for Ethics Committee approval or notification. Any protocol change should be documented as a Protocol Amendment.

11.7 Subject withdrawal

A subject may terminate participation in the study at any time without necessarily giving a reason and without any personal disadvantage. An investigator can stop the participation of a subject after consideration of the benefit/risk ratio. Possible reasons are:

1. Serious adverse events
2. Non-compliance
3. Technical grounds (e.g. participant moves away)
4. Early termination of the study at the request of the steering committee or DSMB.

12 Ownership of data and publication agreements

Ownership of data and publication protocols are outlines in the Clinical Trial Funding Deed.

13 References List

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15.1 Diabetes Distress Scales

PAID-Teen (12 – 16 years)

Which of the following diabetes issues are **currently** a problem for you? Place an X in one box on each line which gives the best answer for you.

		Not a problem	Minor problem	Moderat problen	Somewhat serious problem	Serious problem
1.	Feeling sad when I think about having and living with diabetes?	☐	☐	☐	☐	☐
2.	Not knowing if the mood or feelings I am having are related to my blood sugar levels.	☐	☐	☐	☐	☐
3.	Feeling overwhelmed by my diabetes regimen?	☐	☐	☐	☐	☐
4.	Feeling angry when I think about having and living with diabetes?	☐	☐	☐	☐	☐
5.	Feeling constantly concerned about food and eating	☐	☐	☐	☐	☐
6.	Worrying about the future and the possibility of serious complications?	☐	☐	☐	☐	☐
7.	Feeling upset when my diabetes management is “off track”	☐	☐	☐	☐	☐
8.	Feeling “burned-out” by the constant effort to manage diabetes	☐	☐	☐	☐	☐
9.	Feeling that I am not checking my blood sugars often enough	☐	☐	☐	☐	☐
10.	Feeling unclear about exactly what or how much I should be doing to take care of my diabetes properly	☐	☐	☐	☐	☐
11.	Not feeling motivated to keep up with my daily diabetes tasks	☐	☐	☐	☐	☐
12.	Feeling discouraged or defeated when I see high blood sugar results on my meter	☐	☐	☐	☐	☐
13.	Feeling that my friends or family act like “diabetes police” (e.g. nag about eating properly, checking blood sugars, not trying hard enough)	☐	☐	☐	☐	☐
14.	Feeling like my parents don’t trust me to care for my diabetes	☐	☐	☐	☐	☐
15.	Feeling like I must be perfect in my diabetes management	☐	☐	☐	☐	☐
16.	Missing or skipping blood sugar checks	☐	☐	☐	☐	☐
17.	Feeling that my blood sugars are often swinging wildly, no matter how hard I try	☐	☐	☐	☐	☐
18.	Feeling that I am often failing with my diabetes	☐	☐	☐	☐	☐

	regimen					
19.	Feeling that my parents blame me for blood sugar numbers they don't like.	☐	☐	☐	☐	☐
20.	Feeling that my friends or family don't understand how difficult living with diabetes can be	☐	☐	☐	☐	☐
21.	Feeling that I can't control my eating	☐	☐	☐	☐	☐
22.	Feeling like my parents worry about complications too much	☐	☐	☐	☐	☐
23.	Worrying about my weight	☐	☐	☐	☐	☐
24.	Worrying that diabetes gets in the way of having fun and being with my friends	☐	☐	☐	☐	☐
25	Fitting my diabetes regimen into my day when I'm away from home (e.g. school, work, etc.)	☐	☐	☐	☐	☐
26	Worrying about getting low during a sports activity	☐	☐	☐	☐	☐
27.	Feeling like my parents worry about complications too much	☐	☐	☐	☐	☐

PAID (16 years and older)

Problem Areas in Diabetes

Which of the following diabetes issues are **currently** a problem for you? Place an X in one box on each line which gives the best answer for you.

		Not a problem	Minor problem	Moderate problem	Somewhat serious problem	Serious problem
1.	Not having clear and concrete goals for your diabetes care?	☐	☐	☐	☐	☐
2.	Feeling discouraged with your diabetes treatment plan?	☐	☐	☐	☐	☐
3.	Feeling scared when you think about living with diabetes?	☐	☐	☐	☐	☐
4.	Uncomfortable social situations related to your diabetes care (e.g. people telling you what to eat)?	☐	☐	☐	☐	☐
5.	Feelings of deprivation regarding food and meals?	☐	☐	☐	☐	☐
6.	Feeling depressed when you think about living with diabetes?	☐	☐	☐	☐	☐
7.	Not knowing if your mood or feelings are related to your diabetes?	☐	☐	☐	☐	☐
8.	Feeling overwhelmed by your diabetes?	☐	☐	☐	☐	☐
9.	Worrying about low blood sugar reactions?	☐	☐	☐	☐	☐
10.	Feeling angry when you think about living with diabetes?	☐	☐	☐	☐	☐
11.	Feeling constantly concerned about food and eating?	☐	☐	☐	☐	☐
12.	Worrying about the future and the possibility of serious complications?	☐	☐	☐	☐	☐
13.	Feelings of guilt or anxiety when you get off track with your diabetes management?	☐	☐	☐	☐	☐
14.	Not “accepting” your diabetes?	☐	☐	☐	☐	☐
15.	Feeling unsatisfied with your diabetes physician?	☐	☐	☐	☐	☐
16.	Feeling that diabetes is taking up too much of your mental and physical energy every day?	☐	☐	☐	☐	☐
17.	Feeling alone with your diabetes?	☐	☐	☐	☐	☐
18.	Feeling that your friends and family are not supportive of your diabetes management	☐	☐	☐	☐	☐

	efforts?					
19.	Coping with complications of diabetes?	☐	☐	☐	☐	☐
20.	Feeling “burned out” by the constant effort needed to manage diabetes?	☐	☐	☐	☐	☐

15.2Fear of Hypoglycaemia

Fear of Hypoglycaemia Survey (worry scale) (Ages >17 years)

Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Tick the box that best describes how often in ***the last 6 months*** *you WORRIED about each item because of low blood sugar.*

Because my blood sugar could go low, I worried about…		Never	Rarely	Sometimes	Often	Almost always
1.	not recognising / realising I was having low blood sugar	☐	☐	☐	☐	☐
2.	not having food, fruit or juice available	☐	☐	☐	☐	☐
3.	passing out in public	☐	☐	☐	☐	☐
4.	embarrassing myself or my friends in a social situation	☐	☐	☐	☐	☐
5.	having a hypoglycaemic episode while alone	☐	☐	☐	☐	☐
6.	appearing stupid or drunk	☐	☐	☐	☐	☐
7.	losing control	☐	☐	☐	☐	☐
8.	no-one being around to help me during a hypoglycaemic episode	☐	☐	☐	☐	☐
9.	having a hypoglycaemic episode while driving	☐	☐	☐	☐	☐
10.	making a mistake or having an accident	☐	☐	☐	☐	☐
11.	getting a bad evaluation or being criticised	☐	☐	☐	☐	☐
12.	difficulty thinking clearly when responsible for others	☐	☐	☐	☐	☐
13.	feeling lightheaded or dizzy	☐	☐	☐	☐	☐
14.	accidentally injuring myself or others	☐	☐	☐	☐	☐
15.	permanent injury or damage to my health or body	☐	☐	☐	☐	☐
16.	low blood sugar interfering with important things I am doing	☐	☐	☐	☐	☐
17.	becoming hypoglycaemic during sleep	☐	☐	☐	☐	☐

18. getting emotionally upset and difficult to deal with	☐	☐	☐	☐	☐

Fear of Hypoglycaemia Survey (FHS) © Gonder-Frederick L, 1994

Children's Hypoglycaemic Fear Survey (Ages 12-16 years)

We want to find out more about what low blood glucose makes young people feel. Below is a list of things young people with diabetes sometimes worry about concerning low blood glucose. Tick the number that best describes YOU

I worry about		Never	Rarely	Sometimes	Often	Almost always
1.	not recognising that my blood glucose is low	☐	☐	☐	☐	☐
2.	not having sugary food or drink with me when my blood glucose gets low	☐	☐	☐	☐	☐
3.	passing out in public because of low blood glucose	☐	☐	☐	☐	☐
4.	having a low blood glucose while asleep	☐	☐	☐	☐	☐
5.	embarrassing myself because of low blood glucose	☐	☐	☐	☐	☐
6.	having low blood glucose while I am by myself	☐	☐	☐	☐	☐
7.	looking "stupid" or clumsy in front of other people	☐	☐	☐	☐	☐
8.	losing control because of low blood glucose	☐	☐	☐	☐	☐
9.	no one being around to help me during a hypo/low	☐	☐	☐	☐	☐
10.	making a mistake or having an accident at school	☐	☐	☐	☐	☐
11.	getting in trouble at school because of something that happens when my glucose is low	☐	☐	☐	☐	☐
12.	having seizures	☐	☐	☐	☐	☐
13.	getting long term complications from low blood glucose	☐	☐	☐	☐	☐
14.	feeling dizzy or woozy when my blood glucose is low	☐	☐	☐	☐	☐
15.	having a hypo/low blood glucose	☐	☐	☐	☐	☐

Teen Low Blood Sugar Survey (FHS-T) © Gonder-Frederick L, 1990 (rev 2012)

15.3 General Anxiety

STAI adult (17 years and older)

SELF-EVALUATION QUESTIONNAIRE (PRE) **STAI Form Y-1**

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel **RIGHT NOW**, that is, **AT THIS MOMENT**. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I am tense	1	2	3	4
4.	I feel strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel comfortable	1	2	3	4
11.	I feel self-confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I am jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

MIND GARDEN
Palo Alto, California

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

Participant ID_____

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you **GENERALLY** feel.

		ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21.	I feel pleasant	1	2	3	4
22.	I feel nervous and restless	1	2	3	4
23.	I feel satisfied with myself	1	2	3	4
24.	I wish I could be as happy as others seem to be	1	2	3	4
25.	I feel like a failure	1	2	3	4
26.	I feel rested	1	2	3	4
27.	I am "calm, cool, and collected"	1	2	3	4
28.	I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29.	I worry too much over something that really doesn't matter	1	2	3	4
30.	I am happy	1	2	3	4
31.	I have disturbing thoughts	1	2	3	4
32.	I lack self-confidence	1	2	3	4
33.	I feel secure	1	2	3	4
34.	I make decisions easily	1	2	3	4
35.	I feel inadequate	1	2	3	4
36.	I am content	1	2	3	4
37.	Some unimportant thought runs through my mind and bothers me	1	2	3	4
38.	I take disappointments so keenly that I can't put them out of my mind.	1	2	3	4
39.	I am a steady person	1	2	3	4
40.	I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

 STAIP-AD Test Form Y

STAI child (12 – 16 years)

How do you feel right now, at this moment?

1. I feel	Very calm	Calm	Not calm
2. I feel	Very upset	Upset	Not upset
3. I feel	Very pleasant	Pleasant	Not pleasant
4. I feel	Very nervous	Nervous	Not nervous
5. I feel	Very jittery	Jittery	Not jittery
6. I feel	Very rested	Rested	Not rested
7. I feel	Very scared	Scared	Not scared
8. I feel	Very relaxed	Relaxed	Not relaxed
9. I feel	Very worried	Worried	Not worried
10. I feel	Very satisfied	Satisfied	Not satisfied
11. I feel	Very frightened	Frightened	Not frightened
12. I feel	Very happy	Happy	Not happy
13. I feel	Very sure	Sure	Not sure
14. I feel	Very good	Good	Not good
15. I feel	Very troubled	Troubled	Not troubled
16. I feel	Very bothered	Bothered	Not bothered
17. I feel	Very nice	Nice	Not nice
18 I feel	Very terrified	Terrified	Not terrified
19. I feel	Very mixed-up	Mixed-up	Not mixed-up
20. I feel	Very cheerful	Cheerful	Not cheerful

How do you usually feel?

		Hardly ever	Sometimes	often
1.	I worry about making mistakes	☐	☐	☐
2.	I feel like crying	☐	☐	☐
3.	I feel unhappy	☐	☐	☐
4.	I have trouble making up my mind	☐	☐	☐
5.	It is difficult for me to face my problems	☐	☐	☐
6.	I worry too much	☐	☐	☐
7.	I get upset at home	☐	☐	☐
8.	I am shy	☐	☐	☐
9.	I feel troubled	☐	☐	☐
10.	Unimportant thoughts run through my mind and bother me	☐	☐	☐
11.	I worry about school	☐	☐	☐
12.	I have trouble deciding what to do	☐	☐	☐
13.	I notice my heart beats fast	☐	☐	☐
14.	I am secretly afraid	☐	☐	☐
15.	I worry about my parents	☐	☐	☐
16.	My hand gets sweaty	☐	☐	☐
17.	I worry about things that may happen	☐	☐	☐
18	It is hard for me to fall asleep at night	☐	☐	☐
19.	I get a funny feeling in my stomach	☐	☐	☐
20.	I worry about what others think of me.	☐	☐	☐

15.4General Health Status

EQ 5D-Y (12 – 25yrs)

Health Questionnaire - For Participants ≥12 years

By placing a tick <u>in ONE box in each group</u> below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking around ☐

I have some problems in walking around ☐

I am confined to bed ☐

Personal Care

I have no problems with personal care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐ I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

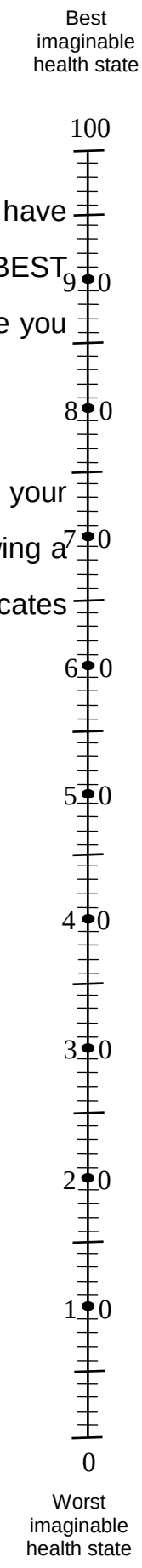
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the BEST state you can imagine is marked 100 and the WORST state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



15.5Diabetes Specific Quality of Life

ID#_____

Date:_____

PedsQL™
Diabetes Module

Version 3.2

CHILD REPORT (ages **8-12**)

DIRECTIONS

Children with diabetes sometimes have special problems. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY DIABETES ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel hungry	0	1	2	3	4
2. I feel thirsty	0	1	2	3	4
3. I have to go to the bathroom too often	0	1	2	3	4
4. I have tummy aches	0	1	2	3	4
5. I have headaches	0	1	2	3	4
6. I feel like I need to throw up	0	1	2	3	4
7. I go "low"	0	1	2	3	4
8. I go "high"	0	1	2	3	4
9. I feel tired	0	1	2	3	4
10. I get shaky	0	1	2	3	4
11. I get sweaty	0	1	2	3	4
12. I feel dizzy	0	1	2	3	4
13. I feel weak	0	1	2	3	4
14. I have trouble sleeping	0	1	2	3	4
15. I get cranky or grumpy	0	1	2	3	4

*In the past **ONE month**, how much of a **problem** has this been for you …*

TREATMENT - I ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It hurts to get my finger pricked	0	1	2	3	4
2. It hurts to get insulin shots	0	1	2	3	4
3. I am embarrassed by my diabetes treatment	0	1	2	3	4
4. My parents and I argue about my diabetes care	0	1	2	3	4
5. It is hard for me to do everything I need to do to care for my diabetes	0	1	2	3	4

*Whether you do these things **on your own or with the help of your parents**, please answer how hard these things were to do in the past **ONE month**.*

TREATMENT - II ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to take blood glucose tests	0	1	2	3	4
2. It is hard for me to take insulin shots	0	1	2	3	4
3. It is hard for me to play or do sports	0	1	2	3	4
4. It is hard for me to keep track of carbohydrates	0	1	2	3	4
5. It is hard for me to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for me to snack when I go "low"	0	1	2	3	4

PedsQL 3

*In the past **ONE month**, how much of a **problem** has this been for you …*

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I worry about going "low"	0	1	2	3	4
2. I worry about going "high"	0	1	2	3	4
3. I worry about long-term complications from diabetes	0	1	2	3	4

*In the past **ONE month**, how much of a **problem** has this been for you …*

COMMUNICATION ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to tell the doctors and nurses how I feel	0	1	2	3	4
2. It is hard for me to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for me to explain my illness to other people	0	1	2	3	4
4. I am embarrassed about having diabetes	0	1	2	3	4

ID#_____

Date:_____

PedsQL™
Diabetes Module

Version 3.2

TEEN REPORT (ages **13-18**)

DIRECTIONS

Teens with diabetes sometimes have special problems. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY DIABETES ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I feel hungry	0	1	2	3	4
2. I feel thirsty	0	1	2	3	4
3. I have to go to the bathroom too often	0	1	2	3	4
4. I have stomachaches	0	1	2	3	4
5. I have headaches	0	1	2	3	4
6. I feel like I need to throw up	0	1	2	3	4
7. I go "low"	0	1	2	3	4
8. I go "high"	0	1	2	3	4
9. I feel tired	0	1	2	3	4
10. I get shaky	0	1	2	3	4
11. I get sweaty	0	1	2	3	4
12. I feel dizzy	0	1	2	3	4
13. I feel weak	0	1	2	3	4
14. I have trouble sleeping	0	1	2	3	4
15. I get cranky or grumpy	0	1	2	3	4

*In the past **ONE month**, how much of a **problem** has this been for you …*

TREATMENT - I ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It hurts to get my finger pricked	0	1	2	3	4
2. It hurts to get insulin shots	0	1	2	3	4
3. I am embarrassed by my diabetes treatment	0	1	2	3	4
4. My parents and I argue about my diabetes care	0	1	2	3	4
5. It is hard for me to do everything I need to do to care for my diabetes	0	1	2	3	4

*Whether you do these things **on your own or with the help of your parents**, please answer how hard these things were to do in the past **ONE month**.*

TREATMENT II - ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to take blood glucose tests	0	1	2	3	4
2. It is hard for me to take insulin shots	0	1	2	3	4
3. It is hard for me to exercise or do sports	0	1	2	3	4
4. It is hard for me to keep track of carbohydrates	0	1	2	3	4
5. It is hard for me to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for me to snack when I go "low"	0	1	2	3	4

PedsQL 3.2 - (13-18) Diabetes
04/09

PedsQL 3

*In the past **ONE month**, how much of a **problem** has this been for you …*

WORRY ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about going "low"	0	1	2	3	4
2. I worry about going "high"	0	1	2	3	4
3. I worry about long-term complications from diabetes	0	1	2	3	4

*In the past **ONE month**, how much of a **problem** has this been for you …*

COMMUNICATION ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to tell the doctors and nurses how I feel	0	1	2	3	4
2. It is hard for me to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for me to explain my illness to other people	0	1	2	3	4
4. I am embarrassed about having diabetes	0	1	2	3	4

ID#_____

Date:_____

PedsQL™
Diabetes Module

Version 3.2

YOUNG ADULT REPORT (ages 18-25)

DIRECTIONS

Young Adults with diabetes sometimes have special problems. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Pae

diatric Specific diabetes quality of life, young adult version (aged 18– 25years)

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY DIABETES ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel hungry	0	1	2	3	4
2. I feel thirsty	0	1	2	3	4
3. I have to go to the bathroom too often	0	1	2	3	4
4. I have stomachaches	0	1	2	3	4
5. I have headaches	0	1	2	3	4
6. I feel like I need to throw up	0	1	2	3	4
7. I go "low"	0	1	2	3	4
8. I go "high"	0	1	2	3	4
9. I feel tired	0	1	2	3	4
10. I get shaky	0	1	2	3	4
11. I get sweaty	0	1	2	3	4
12. I feel dizzy	0	1	2	3	4
13. I feel weak	0	1	2	3	4
14. I have trouble sleeping	0	1	2	3	4
15. I get cranky or grumpy	0	1	2	3	4

*In the past **ONE month**, how much of a **problem** has this been for you …*

TREATMENT - I ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It hurts to get my finger pricked	0	1	2	3	4
2. It hurts to get insulin shots	0	1	2	3	4
3. I am embarrassed by my diabetes treatment	0	1	2	3	4
4. My parents and I argue about my diabetes care	0	1	2	3	4
5. It is hard for me to do everything I need to do to care for my diabetes	0	1	2	3	4

*Please answer how hard these things were to do in the past **ONE month**.*

TREATMENT II - *(problems with…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to take blood glucose tests	0	1	2	3	4
2. It is hard for me to take insulin shots	0	1	2	3	4
3. It is hard for me to exercise	0	1	2	3	4
4. It is hard for me to keep track of carbohydrates	0	1	2	3	4
5. It is hard for me to carry a fast-acting carbohydrate	0	1	2	3	4
6. It is hard for me to snack when I go "low"	0	1	2	3	4

PedsQL 3.2 - (Young Adult) Diabetes 04/09

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PedsQL 3

*In the past **ONE month**, how much of a **problem** has this been for you …*

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I worry about going "low"	0	1	2	3	4
2. I worry about going "high"	0	1	2	3	4
3. I worry about long-term complications from diabetes	0	1	2	3	4

*In the past **ONE month**, how much of a **problem** has this been for you …*

COMMUNICATION ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to tell the doctors and nurses how I feel	0	1	2	3	4
2. It is hard for me to ask the doctors and nurses questions	0	1	2	3	4
3. It is hard for me to explain my illness to other people	0	1	2	3	4
4. I am embarrassed about having diabetes	0	1	2	3	4

15.6Treatment Satisfaction

Participant ID: _____ Participant DOB: ___/___/___ Date: ___/___/___

Diabetes Treatment Satisfaction Questionnaire (change): DTSQc

For the past few weeks you have been taking part in a diabetes treatment study. Five days ago you had a change of treatment.Today we would like to know how your experience of this current treatment during the **past** 5 days has changed from your experience of your usual pump treatment during the **previous** 5 days. (Treatment includes medication and diet).
Please answer each question by circling a number on each of the sales to indicate the extent to which you have experienced changes. If you have experienced no change in satisfaction, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

2. How often have you felt that your blood sugars have been unacceptably high recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

3. How often have you felt that your blood sugars have been unacceptably low recently?

much more of the time now	3	2	1	0	-1	-2	-3	much less of the time now

4. How convenient have you found your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now

5. How flexible have you found your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now

6. How satisfied are you with your understanding of your diabetes?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now

8. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

Please make sure that you have circled one number on each of the scales.

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you found your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you found your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

15.7Impaired awareness of hypoglycaemia

Gold Score Hypoglycaemia Awareness Questionnaire – Participant age >12 years

Do you know when your hypos are commencing? (Circle one only)

Always Aware						Never Aware
1	2	3	4	5	6	7

15.8 Participant reported outcome for Automated Delivery system

INSPIRE Questionnaire for Children (ages 8-12) with Type 1 Diabetes (Baseline)

We would like ask about your thoughts and feelings about using an automated insulin delivery system (**we call it AID for short**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may be better or worse by using **AID**. **For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I will be more hopeful about my future with use of automated insulin delivery (AID).	☐	☐	☐	☐	☐	
2	I will worry less about diabetes with AID.	☐	☐	☐	☐	☐	
3	AID will reduce my family's concerns about my diabetes.	☐	☐	☐	☐	☐	
4	AID will make it easier for me to do the things I want to do without diabetes getting in the way.	☐	☐	☐	☐	☐	
5	AID will decrease how often I have low glucose levels.	☐	☐	☐	☐	☐	
6	AID will decrease how often I have high glucose levels.	☐	☐	☐	☐	☐	
7	AID will help me stay in my target glucose range more often.	☐	☐	☐	☐	☐	
8	AID will improve my A1c to target level.	☐	☐	☐	☐	☐	
9	AID will make it easy to eat when I want.	☐	☐	☐	☐	☐	
10	AID will make it easy to exercise when I want.	☐	☐	☐	☐	☐	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
11	AID will make managing diabetes easy when I am at school.	☐	☐	☐	☐	☐	
12	AID will make managing diabetes easy when travelling.	☐	☐	☐	☐	☐	
13	AID will make managing diabetes easy when I am with my friends.	☐	☐	☐	☐	☐	
14	AID will help me manage sick days.	☐	☐	☐	☐	☐	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
15	AID will help me sleep better.	☐	☐	☐	☐	☐	
16	I believe that I will have fewer lows during the night with AID.	☐	☐	☐	☐	☐	
17	AID will improve my overall quality of life.	☐	☐	☐	☐	☐	
18	AID will improve my family's overall quality of life.	☐	☐	☐	☐	☐	

Thank you for taking part, your answers are very important to us.

INSPIRE Questionnaire for Teenagers with Type 1 Diabetes (Baseline)

We would like ask about your thoughts and feelings about using an automated insulin delivery system (**abbreviated AID**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may be better or worse by using **AID. For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I will worry less about diabetes with AID.	☐	☐	☐	☐	☐	
2	AID will reduce my family's concerns about my diabetes.	☐	☐	☐	☐	☐	
3	AID will make it easier for me do the things that I want to do without diabetes getting in the way.	☐	☐	☐	☐	☐	
4	AID will decrease how often I have low glucose levels.	☐	☐	☐	☐	☐	
5	AID will decrease how often I have high glucose levels.	☐	☐	☐	☐	☐	
6	AID will help me stay in my target glucose range more often.	☐	☐	☐	☐	☐	
7	AID will improve my A1c to target level.	☐	☐	☐	☐	☐	
8	AID will make it easy to eat when I want.	☐	☐	☐	☐	☐	
9	AID will make it easy to exercise when I want.	☐	☐	☐	☐	☐	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
10	AID will make managing diabetes easy when I am at work or school.	☐	☐	☐	☐	☐	
11	AID will make managing diabetes easy when driving (for those who drive) or when traveling.	☐	☐	☐	☐	☐	
12	AID will make managing diabetes easy when it comes to my social life/being with friends.	☐	☐	☐	☐	☐	
13	AID will help me manage sick days.	☐	☐	☐	☐	☐	
14	AID will reduce my risk of long term complications.	☐	☐	☐	☐	☐	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
15	AID will help me sleep better.	☐	☐	☐	☐	☐	
16	I believe that I will have fewer lows during the night with AID.	☐	☐	☐	☐	☐	
17	AID will improve my overall quality of life.	☐	☐	☐	☐	☐	
18	AID will improve my family's overall quality of life.	☐	☐	☐	☐	☐	

Thank you for taking part, your answers are very important to us.

INSPIRE Questionnaire for Adults with Type 1 Diabetes (Baseline)

We would like ask about your thoughts and feelings about using an automated insulin delivery system (**abbreviated AID**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may be better or worse by using **AID. For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I will be more hopeful about my future with use of automated insulin delivery (AID).	◻	◻	◻	◻	◻	
2	I will worry less about diabetes with AID.	◻	◻	◻	◻	◻	
3	AID will reduce my family's concerns about my diabetes.	◻	◻	◻	◻	◻	
4	AID will make it easier for me do the things that I want to do without diabetes getting in the way.	◻	◻	◻	◻	◻	
5	AID will decrease how often I have low glucose levels.	◻	◻	◻	◻	◻	
6	AID will decrease how often I have high glucose levels.	◻	◻	◻	◻	◻	
7	AID will help me stay in my target range more often.	◻	◻	◻	◻	◻	
8	AID will improve my A1c to target level.	◻	◻	◻	◻	◻	
9	AID will make it easy to eat when I want.	◻	◻	◻	◻	◻	
10	AID will make it easy to exercise when I want.	◻	◻	◻	◻	◻	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
11	AID will make managing diabetes easy when I am at work or school.	◻	◻	◻	◻	◻	
12	AID will make managing diabetes easy when driving (for those who drive) or when traveling.	◻	◻	◻	◻	◻	
13	AID will make managing diabetes easy when it comes to my social life/being with friends.	◻	◻	◻	◻	◻	
14	AID will help me manage diabetes when it comes to my sex life.	◻	◻	◻	◻	◻	
15	AID will help me manage diabetes when I choose to drink alcohol.	◻	◻	◻	◻	◻	
16	AID will help me manage sick days.	◻	◻	◻	◻	◻	
17	AID will help me if I am pregnant.	◻	◻	◻	◻	◻	
18	AID will reduce my risk of long term complications.	◻	◻	◻	◻	◻	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
19	AID will help me sleep better.	◻	◻	◻	◻	◻	
20	I believe that I will have fewer lows during the night with AID.	◻	◻	◻	◻	◻	
21	AID will improve my overall quality of life.	◻	◻	◻	◻	◻	
22	AID will improve my family's overall quality of life.	◻	◻	◻	◻	◻	

Thank you for taking part, your answers are very important to us.

INSPIRE Questionnaire for Children (ages 8-12) with Type 1 Diabetes (Post Assessment)

We would like ask about your thoughts and feelings about your experience with using an automated insulin delivery system (**we call it AID for short**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may have been better or worse by wearing an **AID**. **For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I was more hopeful about my future with use of automated insulin delivery (AID).	☐	☐	☐	☐	☐	
2	I worried less about diabetes with AID.	☐	☐	☐	☐	☐	
3	AID reduced my family's concerns about my diabetes.	☐	☐	☐	☐	☐	
4	AID made it easier for me to do the things I wanted to do without diabetes getting in the way.	☐	☐	☐	☐	☐	
5	AID decreased how often I had low glucose levels.	☐	☐	☐	☐	☐	
6	AID decreased how often I had high glucose levels.	☐	☐	☐	☐	☐	
7	AID helped me stay in my target glucose range more often.	☐	☐	☐	☐	☐	
8	AID improved my A1c to target level.	☐	☐	☐	☐	☐	
9	AID made it easier to eat when I wanted to.	☐	☐	☐	☐	☐	
10	AID made it easier to exercise when I wanted to.	☐	☐	☐	☐	☐	
		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
11	AID made managing diabetes easier when I was at school.	☐	☐	☐	☐	☐	
12	AID made managing diabetes easier when traveling.	☐	☐	☐	☐	☐	
13	AID made managing diabetes easier when I was with my friends.	☐	☐	☐	☐	☐	
14	AID helped me manage sick days.	☐	☐	☐	☐	☐	
		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
15	AID helped me sleep better.	☐	☐	☐	☐	☐	
16	I had fewer lows during the night with AID.	☐	☐	☐	☐	☐	
17	AID improved my overall quality of life.	☐	☐	☐	☐	☐	
18	AID improved my family's overall quality of life.	☐	☐	☐	☐	☐	

Thank you for taking part, your answers are very important to us.

INSPIRE Questionnaire for Teenagers with Type 1 Diabetes (Post Assessment)

We would like ask about your thoughts and feelings about your experience using an automated insulin delivery system (**abbreviated AID**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may have been better or worse by using **AID. For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I worried less about diabetes with the AID.	☐	☐	☐	☐	☐	
2	AID reduced my family's concerns about my diabetes.	☐	☐	☐	☐	☐	
3	AID made it easier for me do the things that I wanted to do without diabetes getting in the way.	☐	☐	☐	☐	☐	
4	AID decreased how often I had low glucose levels.	☐	☐	☐	☐	☐	
5	AID decreased how often I had high glucose levels.	☐	☐	☐	☐	☐	
6	AID helped me stay in my target glucose range more often.	☐	☐	☐	☐	☐	
7	AID improved my A1c to target level.	☐	☐	☐	☐	☐	
8	AID made it easier to eat when I wanted to.	☐	☐	☐	☐	☐	
9	AID made it easier to exercise when I wanted to.	☐	☐	☐	☐	☐	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
10	AID made managing diabetes easier when I was at work or school.	☐	☐	☐	☐	☐	
11	AID made managing diabetes easier when driving (for those who drive) or when traveling.	☐	☐	☐	☐	☐	
12	AID made managing diabetes easier when it came to my social life/being with friends.	☐	☐	☐	☐	☐	
13	AID helped me manage sick days.	☐	☐	☐	☐	☐	
14	AID reduced my risk of long term complications.	☐	☐	☐	☐	☐	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
15	AID helped me sleep better.	☐	☐	☐	☐	☐	
16	I had fewer lows during the night with AID.	☐	☐	☐	☐	☐	
17	AID improved my overall quality of life.	☐	☐	☐	☐	☐	
18	AID improved my family's overall quality of life.	☐	☐	☐	☐	☐	

Thank you for taking part, your answers are very important to us.

INSPIRE Questionnaire for Adults with Type 1 Diabetes (Post Assessment)

We would like ask about your thoughts and feelings about your experience using an automated insulin delivery system (**abbreviated AID**), sometimes called a closed loop system, artificial pancreas or bionic pancreas. We would like you to think about living with diabetes and the things that may have been better or worse by using **AID. For each of the questions below, please tick (check) the box that best fits your answer. Please answer every question.**

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
1	I was more hopeful about my future when using an automated insulin delivery (AID).	◻	◻	◻	◻	◻	
2	I worried less about diabetes with AID.	◻	◻	◻	◻	◻	
3	AID reduced my family's concerns about my diabetes.	◻	◻	◻	◻	◻	
4	AID made it easier for me do the things that I wanted to do without diabetes getting in the way.	◻	◻	◻	◻	◻	
5	AID decreased how often I had low glucose levels.	◻	◻	◻	◻	◻	
6	AID decreased how often I had high glucose levels.	◻	◻	◻	◻	◻	
7	AID helped me stay in my target range more often.	◻	◻	◻	◻	◻	
8	AID improved my A1c to target level.	◻	◻	◻	◻	◻	
9	AID made it easier to eat when I wanted to.	◻	◻	◻	◻	◻	
10	AID made it easier to exercise when I wanted to.	◻	◻	◻	◻	◻	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
11	AID made managing diabetes easier when I was at work or school.	◻	◻	◻	◻	◻	
12	AID made managing diabetes easier when driving (for those who drive) or when traveling.	◻	◻	◻	◻	◻	
13	AID made managing diabetes easier when it came to my social life/being with friends.	◻	◻	◻	◻	◻	
14	AID helped me manage diabetes when it came to my sex life.	◻	◻	◻	◻	◻	
15	AID helped me manage diabetes when I chose to drink alcohol.	◻	◻	◻	◻	◻	
16	AID helped me manage sick days.	◻	◻	◻	◻	◻	
17	AID reduced my risk of long term complications.	◻	◻	◻	◻	◻	

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	N/A
18	AID helped me sleep better.	◻	◻	◻	◻	◻	
19	I had fewer lows during the night with AID.	◻	◻	◻	◻	◻	
20	AID improved my overall quality of life.	◻	◻	◻	◻	◻	
21	AID improved my family's overall quality of life.	◻	◻	◻	◻	◻	

Thank you for taking part, your answers are very important to us.

15.9 Human Factors Repeated sampling

Mobile devices offer unique opportunities to capture the real world behaviours and associated well-being states of young people as they are unfolding. They are also more integrated into people's daily functioning (especially for young people) than any other technologies enabling more accurate and objective data to be recorded.
Experience Sampling Methodology (ESM) is the repeated sampling of momentary experiences in the study participant's natural environment(24). ESM provides ecologically valid information on naturally occurring events, experiences and contextual characteristics over time. These details can be used to build individual profiles to study intra- and inter-personal trends over time and have used to understand youth behaviours and experiences and validate retrospective reports. Compared with retrospective surveys ESM more accurately captures affect and emotion associated with the studied event, minimizing recall bias and also maximizing the validity of the measurement by collecting responses from individuals in their natural environments. ESM is therefore particularly useful in the evaluation of intervention efficacy and implementation as it provides a valuable insight into contextual factors which may facilitate or hinder the application of knowledge obtained from the intervention being evaluated. Importantly, ESM is valid for use with young people in a range of contexts, including education settings (24, 25) and can be delivered effectively through familiar communication tools such as mobile device technology(26).

In this study ESM will be used to provide repeated assessments of affective states, attitudes, behaviours and contextual variables at prompted moments.(24, 27). An ESM mobile phone App for smartphone and iPod Touch devices developed by Vella-Brodrick et al will be adapted for use in this study(28). The adapted mobile phone App which is highly intuitive and familiar to young people, will be downloaded to the study participants' device(s) of choice.

The ESM App will use 1 prompt weekly, throughout the study. Significant effort will be put into maintaining the cohorts' interest in completing the question prompts by maintaining close contact with participants throughout the study, and there will be design features to help promote compliance and emotional investment – similar to mechanics used in gameplay. Health care professionals will be prompted on a monthly basis to answer a different set of questions. All data is de-identified. As the health care professionals are not consented participants of the trial, consent is implied by answering the questions in the survey. The following consent statements will preceed the survey questions:

"This mobile application will ask 6 questions on a monthly basis on your expectations and experiences of using the hybrid closed loop system with the study participants. Your individual responses are de-identified. By proceeding with survey you are consenting to your de-identified data collected"

The ESM App will be easy and quick to complete with minimal interference to the participants' current activity (average completion times ~90 s) and will: (a) increase measurement accuracy and minimise memory biases associated with retrospective reporting (b) detect dynamic processes between individuals and their environment through repeated assessments (c) enhance generalisability due to the real-life context of the assessment, (d) reveal knowledge transfer in terms of how frequently participants are utilizing the intervention on a daily basis, and (e) allow triangulation with self-report measures.

This App will measure via a series of questions listed below about the participants' current affect and activation states, social and environmental contexts, valence (positive or negative) of a naturally occurring events e.g.: exercise, meals etc., responses to these events and sources of triggers to responses, as well as a subjective evaluation of the responses used. Responses to these questions will provide detailed information about the individual's use of strategies to naturally occurring events in their daily life and an opportunity for the researchers to identify contextual factors which may contribute or hinder the application of the intervention. The questions as stated below were reviewed by the Consumer Engagement Group at Princess Margaret Hospital.

The App will utilize an likehart scales. Participants are also given the option to limit the time range of signal prompts, between their usual waking and bed times, minimizing disruption to the participants' regular routine.

This methodology will be used to also determine the usefulness of the App to track program participants' use of the technology or other recommended strategies, to identify key areas in which participants were able (or not) to apply taught strategies and other areas requiring further training or support.

Data Analysis: The ESM data which will include multiple data points for each participant on a range of measures, will be analysed using multilevel modelling, with time at Level 1, and individual at Level 2 (as time will be nested within individuals).

QUESTIONS TO BE INCLUDED:

All participants:

Statement: Answer these questions thinking about the last week: Use the number scale to answer as the following:

1 = not at all
2 = a little
3 = moderately
4 = quite a lot
5 = A lot

How interrupted was your sleep due to diabetes?

How confident did you feel about exercising/physical activity?

How confident did you feel about socialising?

How worried have you been about having a hypo?

How much effort did you have to put in to treat or avoid having a hypo?

How worried have you been about spending time with high blood glucose?

How much effort did you have to put in to treat or avoid having high blood glucose levels*?*

How "in control" have you felt of your diabetes?

How much freedom have you felt about your food choices?

How well did you feel you could cope and manage with the things you had to do during the week?

How much would you recommend your current way of giving insulin to others with type 1 diabetes?

Closed loop only:

How often did you look at your pump screen between boluses?

How physically comfortable were you using the technology?

How much did you "trust" the closed loop system?

Have you stopped using the closed loop function?
Yes / No

If YES:
What was the reason you stopped using the closed loop system?
a) Timing of changing the sensor
b) Pump problem
c) Sensor problem
d) Skin problem
e) Personal choice
f) Not managing my glucose levels as well as I want
g) Sport and leisure
h) Other

HEALTH CARE PROFESSIONALS:

The same app platform will be used, but the following set of questions will be posed to the health care professionals involved in the trial (n = 12).

Statement: Answer these questions thinking about the last month: Use the number scale to answer as the following:
1. Strongly disagree
2. Disagree
3. Neither agree nor disagree
4. Agree
5. Strongly agree

Use of Auto Mode makes diabetes care more time consuming for the clinician

I am interested in adopting automated insulin delivery systems into the general clinic

Use of Auto Mode places more burden on the patient compared to standard care

Use of Auto Mode is something most patients could learn to use

Use of Auto Mode will not improve glycaemic outcomes for most patients

Automated insulin delivery is the future of diabetes management

15.10 Biomarker Collection Methodology

Assays required:

Assay	Sample type	Sample size (singliplicate)	Duplicates Analysed?	Comments
CAMs				
sVCAM	EDTA plasma OR serum	20ul	YES	dead volume 100ul
sICAM	EDTA plasma OR serum	20ul	YES	dead volume 100ul
s-eSelectin	EDTA plasma OR serum	30ul	YES	dead volume 100ul
oxLDL	EDTA plasma OR serum	25ul	YES	dead volume 100ul
MPO	EDTA plasma OR serum	25ul	YES	dead volume 100ul
microRNA	EDTA plasma	200ul	NO	
Telomerase				TBA as assessing various assays
DNA methylation	whole blood (EDTA)	1mL	NO	
Glycomark	EDTA plasma OR serum	4ul	NO	dead volume 200ul
Isoprostanes	EDTA plasma OR serum	250ul	NO	
Proteomics	EDTA plasma	50ul	NO	CTC via Aust. Proteomics Facility
Clotting profile	GC/MS EDTA plasma,	400 ul		At CTC (P Hogg)

Collection tubes are assumed to be BD plastic vacutainers with draw volume of 4mL.

.

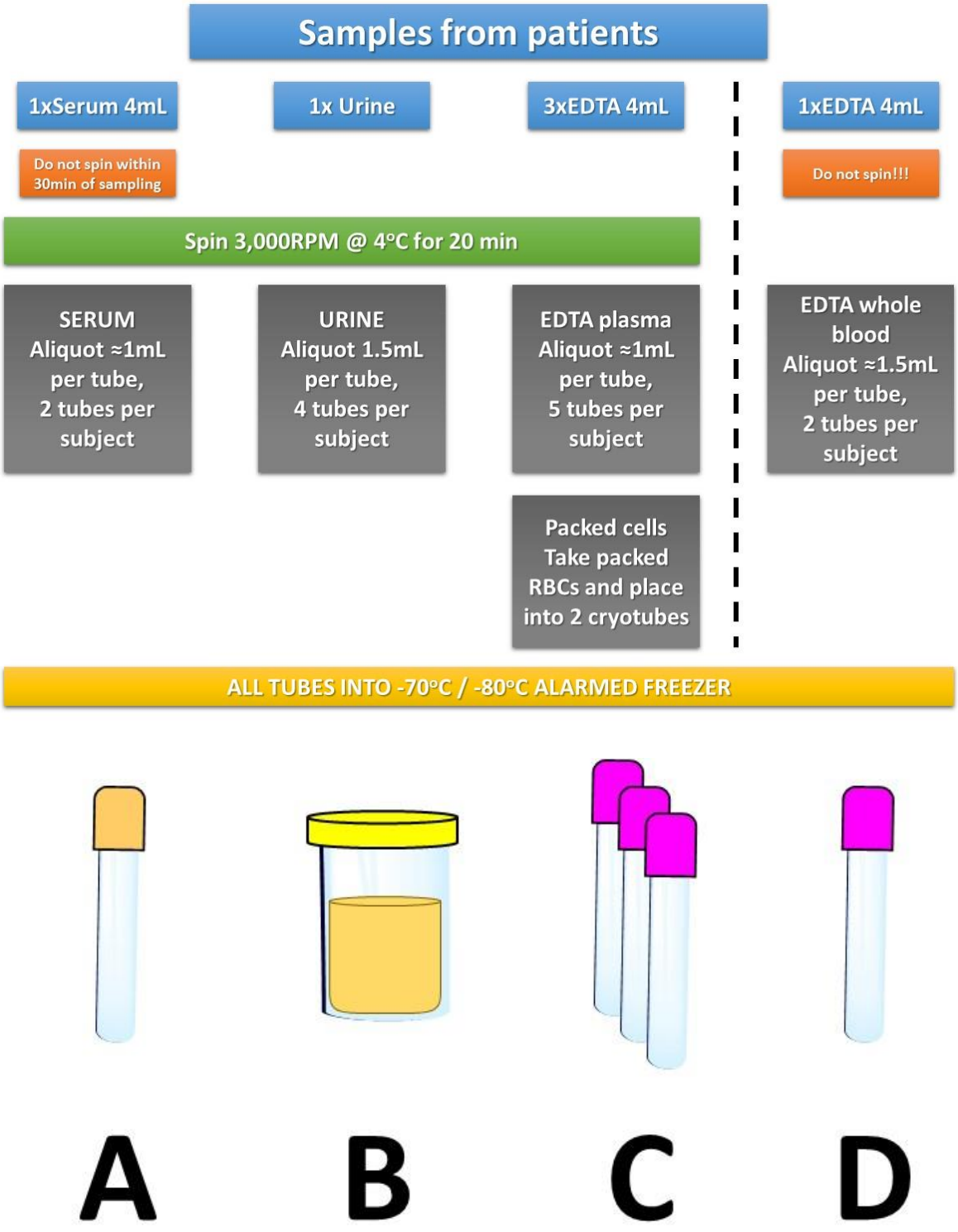
The biomarker samples below are to be collected at baseline and 26 weeks

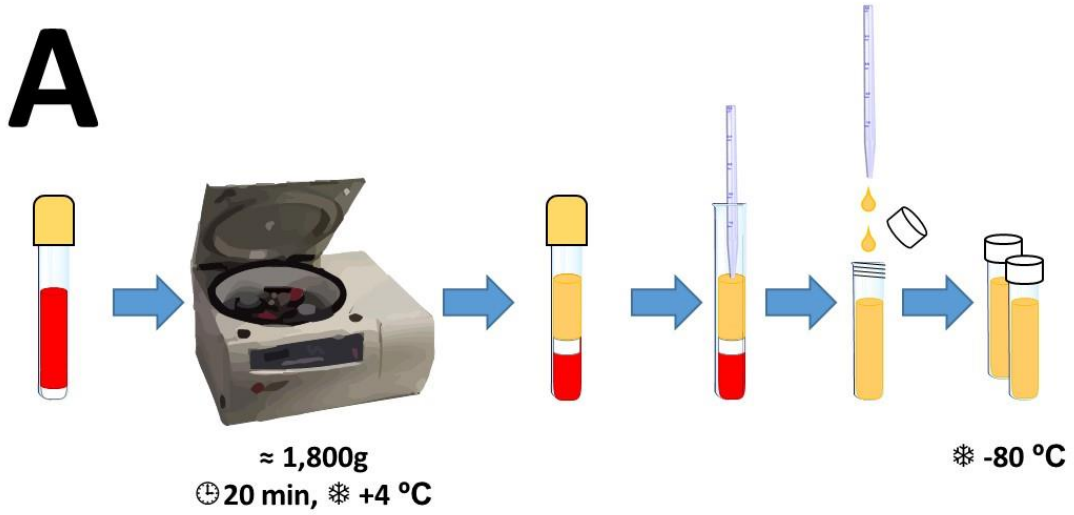
K2EDTA BD catalog number: 367839 (lavender)

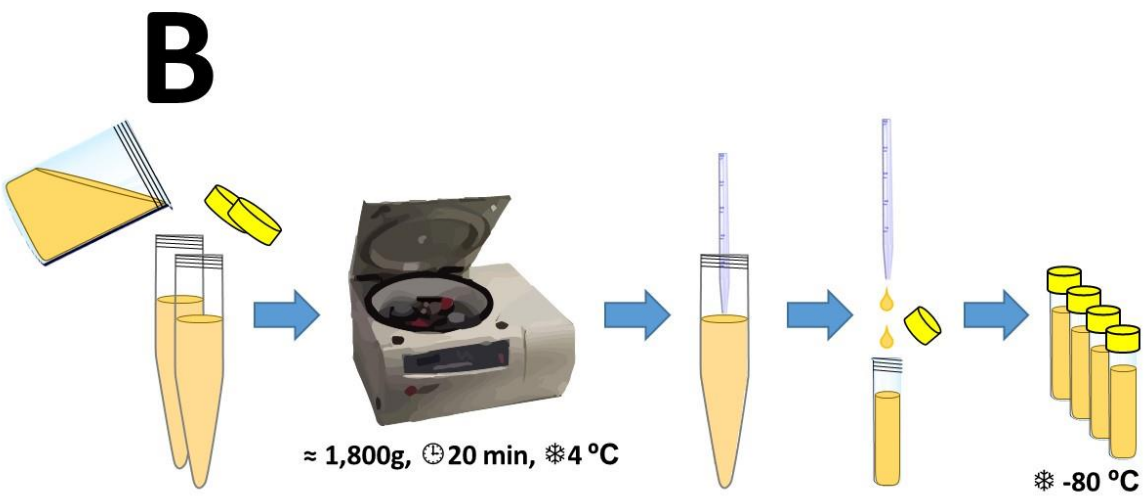
Serum BD catalog number: 367954 (gold) SST (serum separator tube)

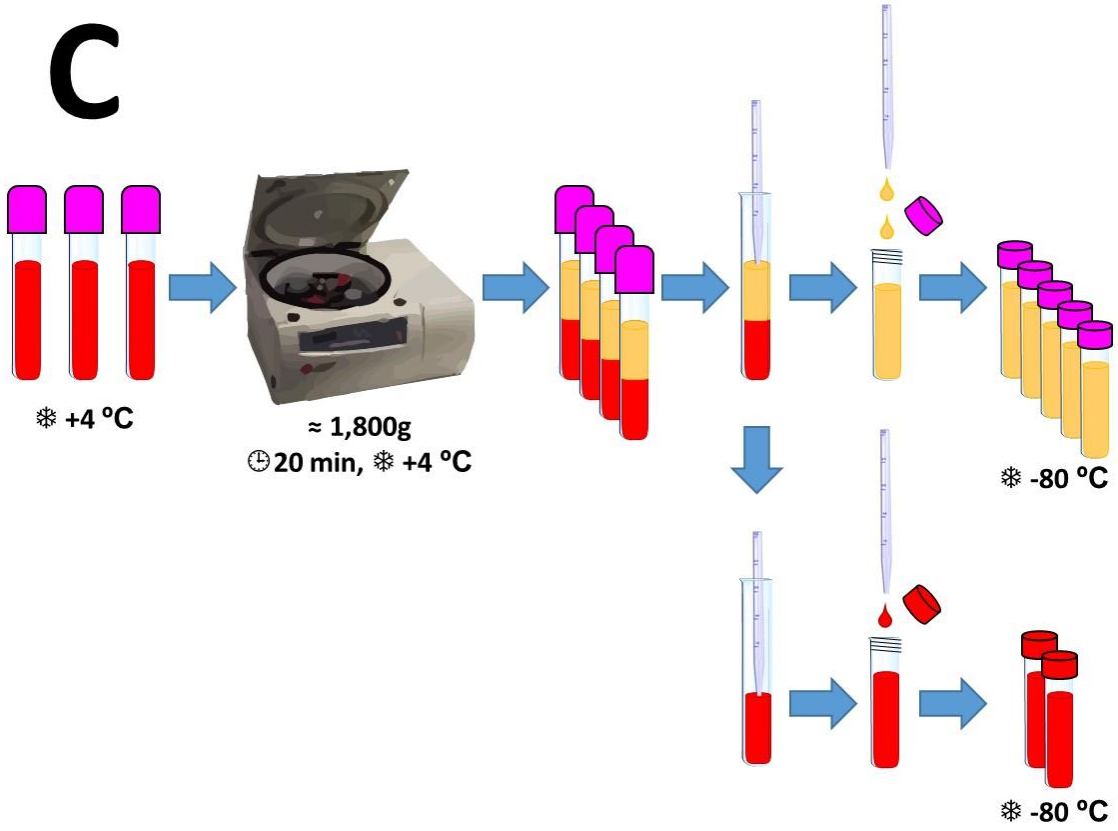
Sample type	Analysis	Tubes for analysis	Biobanking	Tubes for biobanking
Serum			4 mL	1 x 4 mL
EDTA blood	8 mL	2 x 4mL	8 mL	2 x 4 mL
Urine			50 mL	container

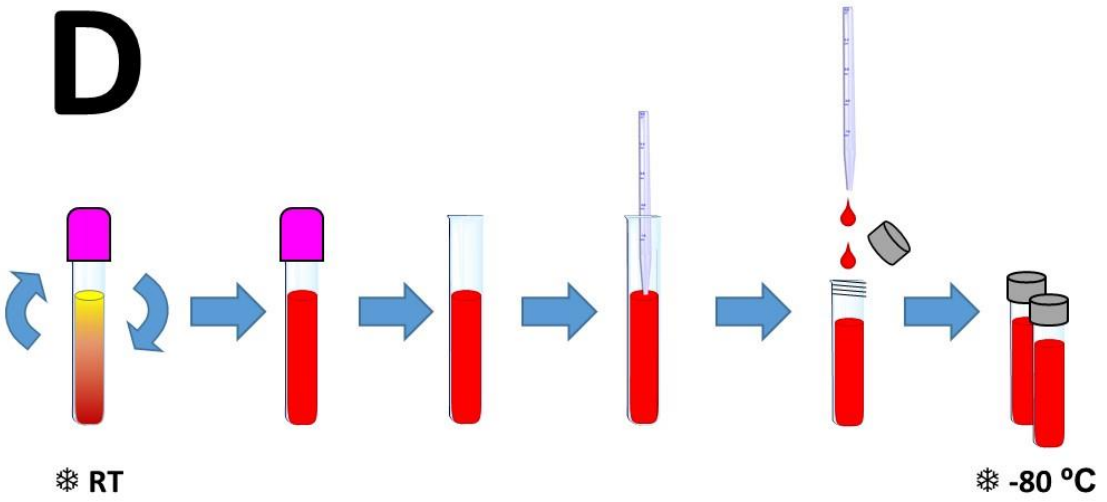
Biomarker samples processing:

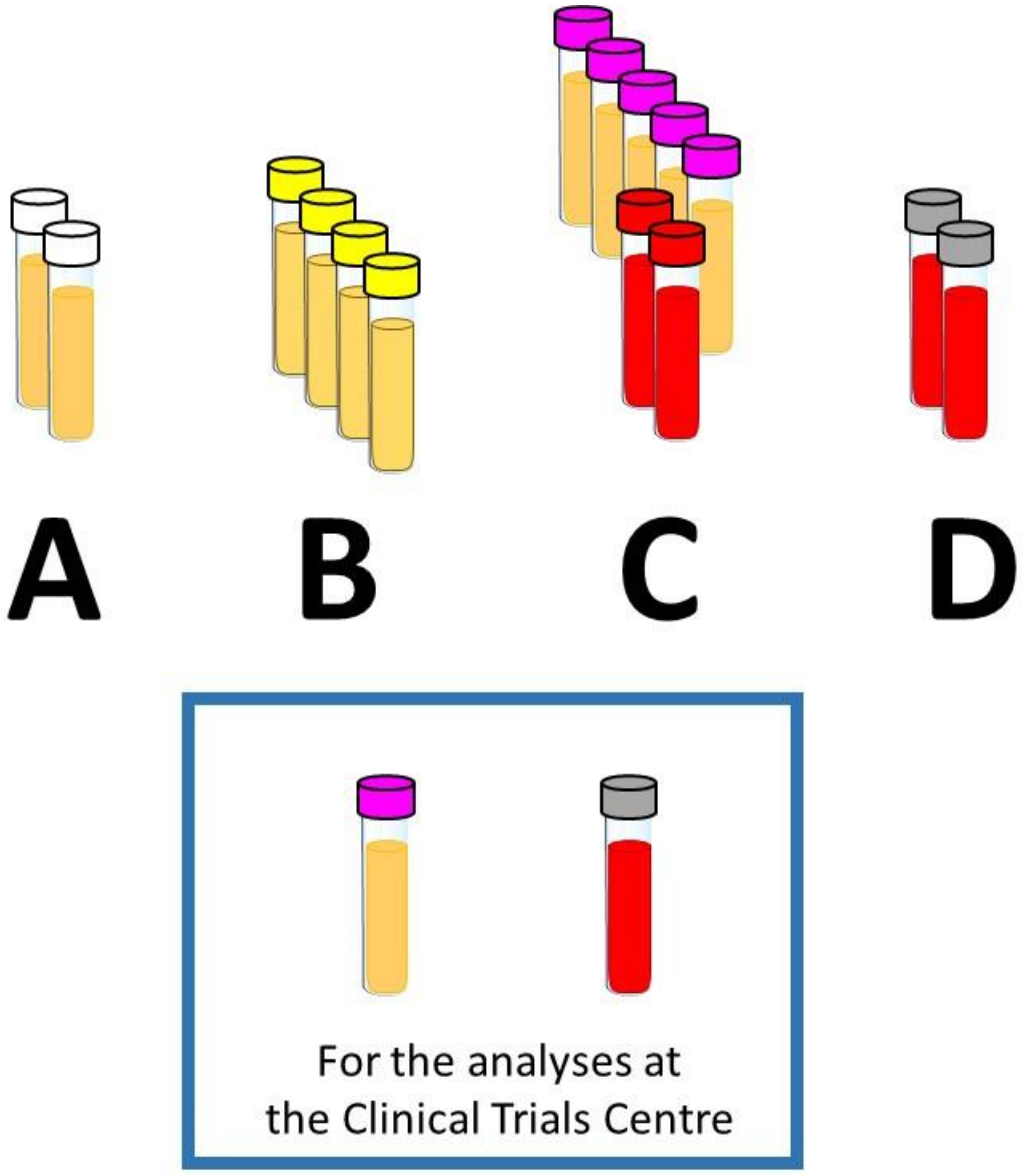



A
≈ 1,800g
20 min, +4 °C
-80 °C


B
≈ 1,800g, 20 min, 4 °C
-80 °C


C
❄ +4 °C
≈ 1,800g
20 min, ❄ +4 °C
❄ -80 °C
❄ -80 °C


D
❄ RT
❄ -80 °C



Remaining aliquots – Biobank at NHMRC Clinical Trials Centre

15.11 Data Safety and Monitoring Board (DSMB): Terms of Reference

To safeguard the interests of the trial participants, monitor the main outcome measure including safety and efficacy, and monitor the overall conduct of the study. The DSMB should receive and review information on the progress and accruing data and provide advice on the conduct of the trial to the Investigators. The DSMB should inform the Lead Investigator if, in their view the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence participant management.

Interim review of the trial's progress including updated figures on recruitment, data quality, adherence to protocol, follow-up, and main outcomes and safety data. Specifically, these roles include to:

1. monitor evidence for differences in the main efficacy outcome measures
2. monitor evidence for harm
3. assess the impact and relevance of external evidence
4. decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant's subgroups
5. decide whether trial follow-up should be stopped earlier
6. assess data quality, including completeness (and by so doing encourage collection of high quality data)
7. maintain confidentiality of all trial information that is not in the public domain
8. monitor recruitment figures and losses to follow-up
9. monitor compliance with the protocol by participants and investigators
10. consider the ethical implications of any recommendations made by the DSMB
11. monitor planned sample size assumptions
12. suggest additional data analyses if necessary
13. advise on protocol modifications proposed by investigators or funders (e.g. to inclusion criteria, trial endpoints, or sample size)
14. monitor continuing appropriateness of participant information
15. monitor compliance with previous DSMB recommendations

Stopping Rules:

The DSMB will be responsible for the points above on a regular basis, and will report to the ethics committees and investigators if stopping the trial is required. Pre-defined stopping rules include:

In general, once a subject is randomized, he/she will remain in the study through the 26-week visit unless the investigator believes it is not safe for the subject to continue. However, the criteria below will be used to determine whether use of the HCL should be discontinued for a subject.

Rules for stopping bionic pancreas use for an individual subject are as follows:
1. Severe hypoglycemia
2. The participant withdraws consent for CHL use
3. Participant pregnancy

4. Noncompliance with the protocol or development of a new medical condition or need for chronic use of a medication which in the judgment of the investigator increases risk for the subject

If HCL use is stopped according to the above criteria, but the subject is willing, they will remain in the trial and will continue to make all of the scheduled visits and participate in all monitoring. The primary analysis will be intention to treat. Since subjects in the usual care arm are following their normal diabetes care regimen, there will be no change in their participation in the trial if they experience one of the events that would trigger stopping..

Study participation is voluntary, and subjects may withdraw at any time.

Criteria for Suspending/Stopping Overall Study

The DSMB will have the responsibility of determining if the overall study should be stopped. In case of a recurring system malfunction or participant safety issue observed with multiple subjects, the overall study will be suspended while the problem is diagnosed. The study may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.
An instance of severe hypoglycaemia in the HCL group will result in temporarily stopping additional enrolment of subjects until DSMB review of the data to determine whether the event was triggered by the system or not and whether it is safe to proceed.
The currently-enrolled subjects will continue use of the system during this time unless the DSMB determines it is unsafe for them to do so.
The overall study will be stopped if the number of participants developing severe hypoglycaemia HCL group exceeds the number in the control Group by 5 or more at any time. However, the DSMB will have the authority to stop the study at any time because of safety concerns even if this criterion is not met.
The Coordinating Centre will track all participant withdrawals. If the above rule is met (HCL Group exceeding control Group by 5 or more), an emergency meeting of the DSMB will be convened within 7 days to review the data. In addition, the DSMB Chair may request a meeting at any time.

15.12 Principal Investigators' Responsibilities

The following responsibilities must be fulfilled by the investigator(s), in terms of GCP requirements and TGA regulatory requirements:

1. Appropriate qualifications for the trial being carried out.
2. Declaration of any conflicts of interest, payments etc. from other parties.
3. Must maintain a list of any delegated duties with respect to the trial, and the persons and qualifications of those persons to whom the duties are assigned.
4. Must be able to demonstrate that adequate subject recruitment is likely to be possible, with necessary time available to conduct the study to GCP requirements, and with adequate facilities and trial staff.
5. Must provide medical care to trial participants that are necessary as a result of any adverse events experienced during or following the trial that are related to the trial.
6. Must possess, prior to trial commencement, a favourable HREC endorsement of trial protocol, participant information and consent documents, recruitment procedures, consent form updates and any other information given to subjects.
7. All trial related documents are subject to HREC review. A regular trial report is also mandatory for provision to the HREC (at least annually, more frequently if the HREC so desires).
8. Ensure local research governance approval is obtained.
9. The trial MUST be conducted according to the approved protocol.
10. Any deviation from the protocol must be documented for later review.
11. No deviation from protocol may occur without HREC endorsement, unless it is required to prevent imminent harm to participants. If the protocol deviation results in the creation of a "separate and distinct" therapeutic good as defined in section 16 of the Therapeutic Goods Act 1989, a new notification is required for CTN or CTX trials.
12. CTN forms notified must be **originals.** A copy should be kept in the Trial Master File.
13. A new CTN is required, or in the case of CTX a new "notification of intent to conduct clinical trial" form, for any new trial site subsequently added.
14. Accountability of the investigational product at the trial site(s).
15. Ensuring subjects have made fully informed, written consent, with all trial procedures and risks adequately explained.
16. Discuss the trial with medical and nursing staff that see eligible participants and ensure they are updated on the current state of knowledge, the trial and its procedures.
17. Report promptly to the coordinating centre any problems in meeting recruitment targets so that support can be provided.
18. Ensure that mechanisms for consent and recruitment are in place.
19. Ensure that data collection forms are completed and returned to the lead centre promptly and to deal with any queries.

20. Make data available for verification, audit and inspection purposes as necessary.
21. Facilitate other aspects of coordination as relevant.
22. Ensure that the confidentiality of all information about trial participants is respected by all persons and that records are kept in areas in which access is restricted.
23. Ensure the trial is conducted in accordance with ICH GCP.
24. Ensure that adverse events are reported in line with statutory guidelines.

15.13 List of abbreviations

AGE	Advanced Glycation End product
CGM	Continuous glucose monitoring
CHO	Carbohydrate
CI	Confidence interval
CRF	Case Record Form
CSII	Continuous subcutaneous insulin infusion
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
DNA	Deoxyribose Nucleic Acid
DSMB	Data Safety and Monitoring Board
GCP	Good Clinical Practice
GST	Glucose Sensor Transmitter
HbAIc	Glycosylated haemoglobin
HCL	Hybrid Closed Loop
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IP	Intellectual property
IQR	Interquartile range
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
JDRF	Juvenile Diabetes Research Foundation
MDI	Multiple Daily Injection
PC	Personal Computer
PI	Principal Investigator
PID	Proportional Integrative Derivative
PM	Project Manager
QALY	Quality Adjusted Life Year
QC	Quality control
RCT	Randomized controlled trial
RNA	Ribosomal Nucleic Acid
SAE	Serious Adverse Event
SD	Standard deviation
TGA	Therapeutic Goods Administration (Australia)
TID	Type 1 diabetes

15.14 Protocol Authorisations and Signatures

1. Professor Tim Jones, Lead Investigator

Signature:

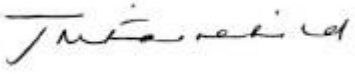
Date: 01/02/2017

2. A/Professor Elizabeth Davis, Principal Investigator

Signature:

Date:01/02/2017

3. Dr Jan Fairchild, Principal Investigator

Signature: 

Date: 01/02/2017

4. Professor Fergus Cameron, Principal Investigator

Signature: Fergus Cameron

Date: 01/02/2017

5. A/Professor Bruce King, Principal Investigator

Signature:

Date: 01/02/2017

6. Professor Geoff Ambler, Principal Investigator

Signature:
Date: 01/02/2017