PROTOCOL

Advanced Hybrid Closed Loop to Improve Glycaemic Control

1. Trial Details

1.1   Trial Details.

Protocol/Clinical Trial Full Title:	The use of an advanced hybrid closed loop system in the management of individuals with type 1 diabetes and sub-optimal glycaemic control		
Short Title:	HCL to Improve Glycaemic Control		
Protocol Number (Version and Date):	V17 31Aug2023		
Trial Start Date:	08/01/2020	Trial Finish Date:	01/05/2023
Coordinating Principal Investigator Name:	Prof Timothy W Jones		
Coordinating Principal Investigator Contact Details:	Tim.jones@health.wa.gov.au 64562222		
Sponsor Name (if applicable):	Telethon Kids Institute		
ANZCTR:	ACTRN12619001452189		

1.2   **Trial Summary (less than 300 words) including background, objectives and trial plan.**
Individuals with Type 1 diabetes (T1D) and sub-optimal glycaemic control are at high risk of developing diabetes complications. This burden of chronic disease and poor health can negatively impact the individual and the family and incurs high health care costs on health care systems and the community. Hence, it is vital to devise interventions to improve glycaemic control and potentially reduce the burden of chronic disease management.

The objective of this project is to utilize an automated insulin delivery (advanced hybrid closed loop) system to improve glycaemic control. Advanced Hybrid Closed Loop (AHCL) system has an automated insulin delivery dependent on sensor glucose readings; although it requires the user to administer meal boluses. HCL therapy was safe during in-home use by adolescents and adults with increased time in target, and reductions in HbA1c, hyperglycaemia and hypoglycaemia, compared to baseline. These results are encouraging and hence it would be valuable to test the effectiveness of HCL in patients with poor glycaemic control and this will be the first trial in this high risk subgroup of patients. This AHCL version includes automatic correction boluses.

We hypothesise that the automated insulin delivery will circumvent the significant glycaemic excursion associated with conventional therapy in patients with poor glycaemic control. Reduced adherence to diabetes self-management tasks is often associated with poor glycaemic control and this trial will address, in effect, the important question as to whether the challenge of managing AHCL is less than the challenge of routine treatment and will generate data that will inform approaches to enhance adherence.

We propose a 6 month multi-centre randomised controlled parallel design study (n=50) assessing the effect of AHCL in adolescents with sub-optimal glycaemic control and comparing this technology with standard care. The primary aim is to compare the change in HbA1c levels during 6 months of therapy with AHCL vs conventional therapy. Secondary outcomes (glycaemic, psychosocial, human factors analysis and health economics) will be measured and analysed.

2. Rationale / Background

2.1   Summary of findings from previous clinical and non-clinical projects, relevant to this proposed trial. Include references to literature and data that are relevant to the trial and that provide background for the trial. *List references separately at the end of the protocol.*

The incidence of type 1 diabetes (T1D) is increasing by around 3% each year with a prevalence of 1 in 300 (1). Despite modern treatment, complications of T1D and a reduced life expectancy continue to be a reality for patients. 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(2). Individuals with T1D and poor glycaemic control are at high risk of developing diabetes complications (3) both in the short term (psychosocial stress, educational impact, hospitalisations for diabetic ketoacidosis or severe hypoglycaemia), and in the long term (for example kidney failure, blindness, heart disease, and peripheral vascular disease requiring amputations). This burden of disease would thereby incur higher health care costs. An increase in HbA1c by 1-percentage-point will, on average, lead to a 6.0% increase in diabetes-related medical costs for type 1 diabetes (4). Attempts to aggressively manage blood glucose levels in order to avoid long-term complications are limited by the fear of hypoglycaemia and anxiety for patients and their caregivers, affecting quality of life, and promoting behaviours aimed at avoiding hypoglycaemia. These actions lead to hyperglycaemia, placing patients at higher risk of developing long term complications. Likewise, T1D 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 (5). Patients with poor glycaemic control are likely to disproportionally contribute to healthcare costs. For all these reasons, it is essential to develop new therapies and device interventions that can improve glycaemic control in this patient group to reduce the burden of disease both on the patient and community.

We recently demonstrated that continuous subcutaneous insulin infusion (CSII) is an effective tool in providing sustained glycaemic improvement in adolescents on multiple daily insulin injections willing to trial insulin pump therapy. The cohort had a reduction of HbA1c by 1.5% at 12 months (de Bock et al, accepted JDST 2018). Hence, as future technologies such as hybrid and fully closed-loop systems become available, patients with sub-optimal glycaemic control should be considered for inclusion in clinical trials, as by virtue of their baseline HbA1c as they potentially have the most to gain.

Closed-Loop technology integrates continuous measurement of interstitial glucose levels from a glucose sensor, a pump for delivering insulin and an algorithm that determines insulin delivery without patient intervention. It offers the potential to circumvent the significant glycaemic excursions associated with conventional therapy. Superior glycaemic control has been demonstrated in many in-clinic studies, diabetes camp studies, hotel studies, short term and long term outpatient studies with lower rates of hypoglycaemia when compared to current diabetes management strategies (6-11). Hybrid closed loop (HCL) has an automated insulin delivery based on sensor glucose feedback system; still requiring the user to administer mealtime bolus insulin. HCL therapy was safe during in-home use by adolescents and adults with increased time in target, and reductions in HbA1c, hyperglycaemia and hypoglycaemia, compared to baseline (7). We have 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 (12, 13). We are currently investigating the Medtronic 670G (version 3.0) hybrid closed loop system in a large multicentre trial in Australia, comparing it's efficacy to standard treatment, and assessing a wide range of outcomes (2016087EP). This study will use the Medtronic 670G 4.0, which includes an updated (advanced hybrid closed loop AHCL) algorithm. The 670G Version 4.0 (AHCL) insulin pump is based on the FDA approved/CE Marked 670G insulin pump. The 670 Version 4.0 (AHCL) insulin pump uses the same hardware as the 670G pump and includes the enhancements relative the the 670G pump listed in section 2.2. In view of the recall on Medtronic Minimed™ 670G 4.0 insulin pumps with clear retainer rings, the study will use the Medtronic Minimed™ 780G insulin pump with the same algorithm, which has the added feature of bluetooth connectivity to allow remote monitoring of glucose levels. For the trial, to maintain the same functionality of the pump, we will use the MiniMed™ 780 pump without using bluetooth feature.

The use of closed loop technology has not been assessed for patients with poor glycaemic control and this will be the first trial in this important subgroup of patients. **This proposal explores the hypothesis that automated insulin delivery will result in improved glycaemic control.** This is an important patient group to study, as they have the greatest potential for improvement in glycaemic outcomes. Individuals in this high risk group also have the potential for improved wellbeing and reduced burden of disease from diabetes complications and health economic impacts which will be analysed in the study. We will explore the impact of this system on quality of life, fear of hypoglycaemia, diabetes distress and acceptance and satisfaction with the use of diabetes technology. Data will be collected to quantify the economic impact of AHCL compared to standard therapy and extrapolated.

The trial will also look into the potential risks with AHCL therapy. The risk of poor treatment adherence by this group will be closely monitored and will address the hypothesis of whether the challenge of managing AHCL therapy is less than the challenge of routine treatment and will generate data that will inform the clinical indications for different diabetes management regimens and delivery of diabetes education in an era of rapidly advancing technology. Acute deterioration in diabetic retinopathy is a known potential risk when glycaemic control is rapidly optimised, as such this will be closely monitored in the trial (14).

Vascular complications are a major cause of morbidity and premature mortality in people with diabetes, due to traditional (adiposity, dyslipidaemia, hypertension, smoking, poor glycaemic control) and novel vascular disease risk factors (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 like 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 individuals with poor glycaemic control. Improved metabolic control may at least partially reduce adverse risk factor profiles. Furthermore, we have cross-sectional data demonstrating improved vascular function and a less adverse novel vascular risk profile in insulin pump treated T1D patients and evidence that molecular markers can be improved by existent and emerging drug therapies.

2.2   Name and description of the intervention or product(s) used in this trial, including investigational product(s) and comparator product/s (if applicable). Include status of product registration (i.e. registration on Australian Therapeutic Goods Registry, or equivalent).

The **Medtronic advanced hybrid closed loop system** is an investigational device which compromises an advanced closed loop algorithm with the compatible, glucose sensor and glucose sensor transmitter.

The algorithm uses a modified proportional integrative derivative (PID) model, with insulin feedback and additional safety features. The algorithm receives glucose data every 5 minutes from the sensor, 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's carbohydrate ratio.

The system in Manual Mode can be programmed to automatically suspend basal insulin delivery for up to two hours when the sensor glucose falls below a predefined or predicted threshold value. In Auto Mode, the system can be programmed to automatically calculate the insulin dose based on information received from continuous glucose monitoring (CGM).

The AHCL has the following enhancements from the commercial Medtronic 670G pump with HCL:

- Additional setpoint option of 5.6 mmol/L (in addition to 6.7 mmol/L and temp target of 8.3 mmol/L). Correction target is 6.7 mmol/L for both 5.6 mmol/L and 6.7 mmol/L setpoints.
- Automatic correction bolus delivery when the pump has been delivering at the maximum allowable basal rate and sensor glucose remains elevated above the correction target when pump is in Auto Mode
- Ability to make therapy adjustment based on sensor glucose values without the requirement for a confirmatory self-monitoring blood glucose (SMBG) measurement
- Other updates to the Auto Mode algorithm intended to reduce the frequency of exits from Auto mode and further minimize glucose excursions.

The MiniMed™ 670G Version 4.0 (AHCL) insulin pump uses the same hardware as the MiniMed™ 670G pump with the advanced algorithm. In view of the recall on insulin pumps with clear retainer rings, the study will use the 780G insulin pump with the same algorithm, which has the added feature of bluetooth wireless communication with the compatible devices in the MiniMed™ 780G System connectivity.

The MiniMed™ 780G Pump works with the following major components: 1) Continuous Glucose Monitoring (CGM) that includes the Guardian Link (3) Transmitter that is connected to the Guardian Sensor (3) to receive sensor glucose values at 5 minute intervals; 2) blood glucose meter (Roche Accu-Chek®) that will be used to calibrate the sensor and has the ability to send blood glucose values

wirelessly as a convenience to the user; 3) MiniMed™ Clinical App to allow upload of data wirelessly, for sharing of glucose levels

To maintain the same functionality as the 670G 4.0 pump for the trial, we will not be using the Minimed™ Clinical App.

Glucose monitoring: All participants will be issued with the CONTOUR® NEXT LINK 2.4 from Bayer. This glucose monitor requires CONTOUR PLUS test strips.
Participants randomised to AHCL will be issued with a study meter, Roche Accu-Chek®, this allows for data to be directly sent to the MiniMed 780G insulin pump.

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.
The MiniMed™ 780G can be uploaded to CareLink via the Blue Adaptor (also know as the BLE dongle). The Blue Adapter is a commercial-off-shelf-component provided by Career Technologies. The Medtronic accessory number is ACC-1003911. The Blue Adapter is not a medical device thus no labeling is needed. Insulin pump data is then accessible for download by the investigators.

Blinded CGM will be collected twice during the study (baseline –for two weeks, and for two weeks at the end of the study). A 4th generation sensor will be inserted and a glucose transmitter connected. Participants will be required to record finger prick glucose levels at least four times a day. CGM data is collected by uploading the transmitter and finger prick values from the CONTOUR® NEXT LINK 2.4 from Bayer.

3. Trial Aims / Objectives / Hypotheses

3.1   Detailed description of the specific primary and secondary objectives and the purpose of the trial. Describe any hypotheses that will be tested.

Aims
The primary aim of the study is
1) To determine the effect of hybrid closed loop on the change in glycated haemoglobin (HbA1c) in adolescents with suboptimal glycaemic control (HbA1c>8.5%) and comparing this technology with standard care.

The secondary aims of the study are
2) To determine the effect of hybrid closed loop on percentage time in range compared to standard therapy
3) To determine the effect of hybrid closed loop on *psychological and social well-being* compared to standard care
4) To determine the effect of hybrid closed loop on glycaemic parameters on hypoglycaemia and hyperglycaemia compared to standard therapy
5) To determine the effect of hybrid closed loop technology on *retinopathy*
6) To determine the effect of hybrid closed loop technology on the *metabolic biomarkers*
7) To determine the *cost effectiveness* of hybrid closed loop technology compared to standard therapy in long term.
8) To determine the *technology–user" interactions* ("human factors") to improve translational strategies

Hypotheses:
1) HCL will improve glycaemic control as assessed by HbA1c.
2) HCL will have a positive impact on quality of life and fear of hypoglycaemia as determined by participant/parent questionnaires.
3) Closed loop technology by improving control could potentially deteriorate retinopathy
4) HCL will be a cost-effective intervention for the management of type 1 diabetes compared to standard treatment.

4. Trial Design

The scientific integrity of the trial and the credibility of the trial data depend substantially on the trial design and methodology.

4.1 Primary endpoints and the secondary endpoints, if any, to be measured during the trial and how they will be measured. *For further information refer to the TGA* "Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)" 2000.

Primary endpoint:

A) Glycaemic control as measured by change in HbA1c collected at baseline, 3 and 6 months post randomisation

Secondary endpoints

B) *Psychosocial well-being*
1) Functional health status EQ-5D-3L (12 to ≤25yrs)
2) Diabetes specific quality of life: PedsQL – Child version (<13 yrs), Adolescent version (13 to <18yrs) and young adult version (18 to ≤25yrs).
3) Fear of hypoglycaemia: Hypoglycaemic Fear Survey-II Worry scale: 17-≤25years. Children's Hypoglycaemia Fear survey 12 to <17yrs.
4) Impact and Satisfaction: The Diabetes Technology Questionnaire, Baseline and Follow-up version (all ages)
5) Diabetes distress: Problem Areas in Diabetes (Paediatric version 12 to <18yrs, Standard version ≥18yrs, Parent version)
6) Hypoglycaemia Awareness: Hypoglycaemia Awareness Scale (Gold Score) (all ages)
7) Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 (12 to 25 years)
8) INSPIRE: Perceived benefits and burdens of automated insulin delivery (all ages – Intervention only)
9) Physical activity: The Active Australia Survey (all ages)
10) Semi structure interview (all ages – post study only)

C) *Glycaemic outcomes:*
    -Percent time in range

D) -CGM data: (time in hypoglycaemia, time in range, and time in hyperglycaemia)
    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

E) Changes in retinopathy scores and retinal microvascular structure (arteriolar or venular dilation, increased vascular fractal dimension, branching and tortuosity)

F) *Human factors:*
    Describe participant technology interaction, adherence patterns and approaches to improve interaction.

G) *Health-economic*
    Report the health economic impact of the MiniMed™ 670G / 780G Insulin Pump Hybrid Closed Loop System Vs standard therapy. The following data points will be used as part of the economic analysis:
    1) QALYs calculated from the EQ-5D-3L
    2) Hypoglycaemic events and HbA1c
    3) Participant reporting on work interruption
    4) Investigator reporting time spent on training, education and support, by the type of health professional resource used
    5) Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin).

4.2   Type (e.g. phase, pilot) and design (e.g. double-blind, placebo-controlled, parallel design) of the trial to be conducted and a schematic diagram of the trial design, procedures and stages (e.g. initial assessment, run-in, pre-randomisation assessment, randomisation, treatment phase, end-of-treatment assessment, washout, cross-over, alternative treatment, post-treatment assessments, trial exit).

This is a **prospective multicentre randomised controlled, two-arm unblinded, parallel study** in free-living conditions, in adolescents with type 1 diabetes on insulin pump therapy. Participants are randomized in two groups; either the control group (standard therapy) or the intervention group (advanced hybrid closed loop). The control group will be participants on insulin pump therapy with or without CGM (continuous glucose monitoring).

AHCL arm: Medtronic MiniMed™ 670G 4.0 / 780G for 6 months
OR
Conventional arm: Standard care for 6 months.
This will be followed by an optional extension phase for another 6 months.

The study will be conducted at four tertiary paediatric diabetes centres (Perth Children's Hospital, WA, Westmead Children's Hospital, NSW, Women's and Children's Hospital, SA, and Royal Children's Hospital, VIC). A home visit may be offered for some visits which involve insertion or return 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.

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

All participants on CGM are encouraged to wear their sensor in the weeks preceding Visit 1.

VISIT 1: 1-2 hrs . (Eligibility Confirmation, Baseline data collection).

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 in Section 5.2. All post menarche females will have a urine βHCG test to exclude pregnancy. The following data will be recorded:

1. Consent signed by participant and investigator
2. Auxological
    a. Height
    b. Weight
    c. BMI
    d. Blood pressure
3. Demographic
    a. Date of Birth
    b. Gender
4. Diabetes clinical
    a. Date of diagnosis
    b. C-peptide (<0.1nmol/L cut off within 3 month of screening visit)
    c. HbA1c
    d. βHCG for all post menarche females
    e. History of severe hypoglycaemia – coma or convulsion or episodes requiring third party assistance (events in last 12 months).
    f. History of diabetic ketoacidosis in the last 12 months
    g. Hospital admissions in the last 12 months (DKA, Hyperglycaemia, Hypoglycaemia, Non diabetes related)
    h. Total daily dose of insulin (mean of previous 7 days)
    i. Co-morbidities and medications
    j. Smoking and alcohol intake
    k. Sensor data in the 2 weeks prior to the study (in participants on CGM).

5. Psychology measures:
    Psychological scales will be administered on an electronic platform.
    a. Functional health status: Quality of Life: EQ-5D-3L for 12 to ≤25yrs
    b. Diabetes specific quality of life: PedsQL Child version (<13 yrs), Adolescent version (13 to <18yrs) and young adult version (18 to ≤25 yrs)

    c. Fear of hypoglycaemia: Hypoglycaemic Fear Survey-II Worry scale: 17 to ≤25yrs. Children's Hypoglycaemia Fear survey 12 to <17 yrs.

    d. Impact and Satisfaction: Diabetes Technology Questionnaire, Baseline version (all ages)

    e. Diabetes distress: Problem Areas in Diabetes (Paediatric version 12 to <18 yrs, Standard version ≥18 yrs, Parent version)

    f. Hypoglycaemia Awareness: Hypoglycaemia Awareness Scale (Gold Score) (all ages)

    g. Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 (12 to 25 years)

    h. Physical activity: The Active Australia Survey (all ages)

6. Insertion of the first blinded CGM (4th generation sensor and transmitter) to collect baseline glycaemic data. This constitutes first of the two sensors, each sensor provides data for 7 days. Participants will be instructed to test minimum 4x/day using CONTOUR® NEXT LINK 2.4 glucometer. At this visit, all participants will be provided with CONTOUR® NEXT LINK 2.4 glucometer and a participant record book

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Figure 1: Schematic representation of the study design

*CGM data from participants on CGM
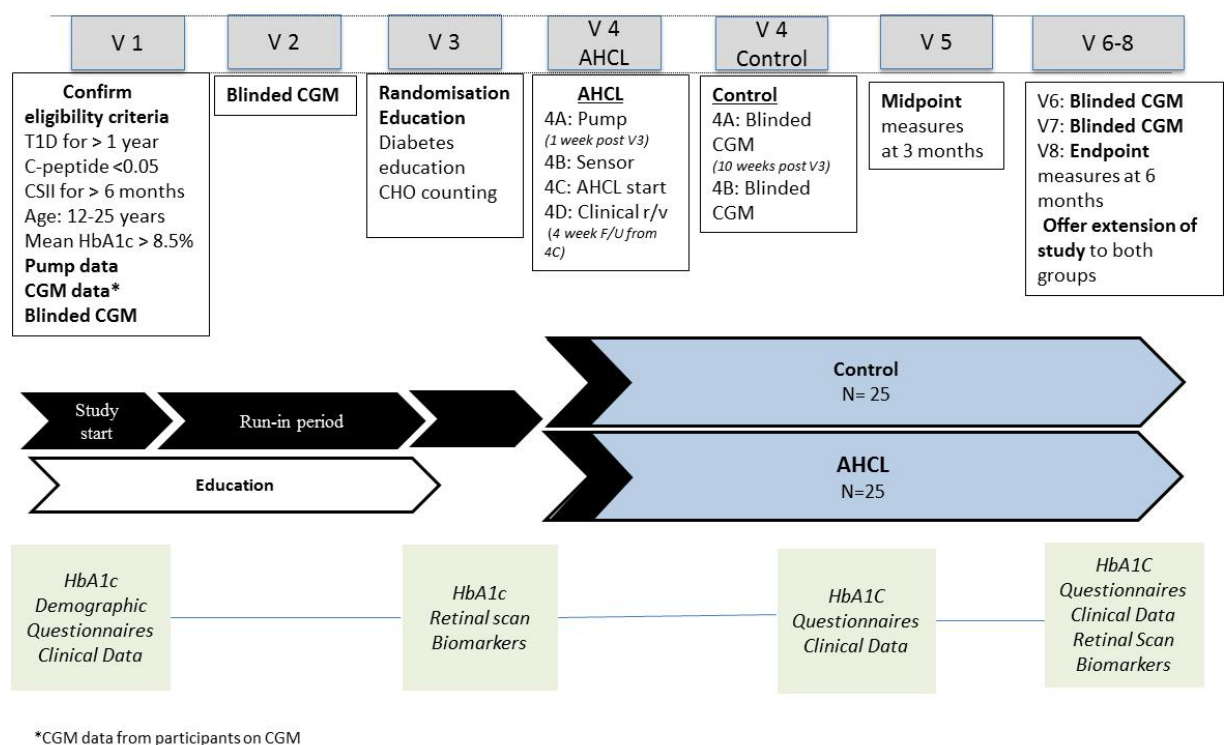
VISIT 2

Visit 2A: Insertion of 2nd blinded CGM
Participants will return 7 days after sensor insertion 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 transmitter attached.

VISIT 2B: The blinded CGM is removed a week after insertion.

If the first or second sensor fail and/or the total readings are <70% for 10 days, a supplemental visit will be organised for a third sensor. Participants are not to have more than 4 sensors for the study. If the maximum of 4 sensors is reached and the required valid sensor glucose readings are not obtained during the run-in period, participant will be withdrawn from the study.

VISIT 3 (4-6 hours)

This visit is the randomisation visit, and allocation is dependent on the stratifications detailed in Section 4.3.

The following data will be collected prior to randomisation:
1. Diabetes clinical
   a. HbA1c
   b. Total daily dose of insulin (mean of previous 7 days)
   c. Severe hypoglycaemia in the run-in period
   d. Diabetic ketoacidosis in the run-in period
   e. Admissions in the run-in period
   f. Pump upload
   g. Sensor data in the 2 weeks prior to the study (in participants on CGM)
2. Diabetes education/review
   a. Diabetes education: Diabetes educator session (2 to 4 hrs) as refresher to re-educate and optimise standard diabetes management
   b. Carbohydrate Counting: Dietician review (1 to 2 hours)
      The duration of the session is variable according to the prior knowledge of the participant.
3. Retinal photographs, will be collected and retained for centralised assessment
4. INSPIRE questionnaire (baseline for participants randomised to AHCL)
5. Medtronic AHCL System Background Patient Questionnaire (optional)
6. Biomarkers
   A detailed description of sample preparation for biomarkers is found in appendix
   12mL of blood and 50mL of urine will be collected in fasting state
   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

VISIT 4 (participants randomised to AHCL arm)

CSII to AHCL: Participant 780G, CGM education and AHCL training.
Visit 4A: Pump training (2 hours)
Participants will be trained on how to use the Medtronic 780G insulin pump. Participants will be provided with Roche Accu-Chek®glucometer along with the glucose strips for the study.

Visit 4B: CGM training (2 hours)
They will be instructed on how to link CGM on the Medtronic 780G pump and issued with Guardian Sensor 3 and the Guardian Link 3 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. Sensor naïve individuals will have familiarisation phase of 7 to 10 days to get used to wearing a sensor. Visit 4A and 4B could be combined for participants familiar with sensors.

Visit 4C: Commencement of AHCL (1 hour)
Once CGM data has been established for a minimum of 3 to 7 days, participant returns for face-to-face instruction on AHCL use and initiation of Automode. During this visit, the sensor will be replaced to demonstrate sensor warm up and AHCL initiation, and provide an opportunity for those unfamiliar with CGM use to practice a sensor change with supervision. Upon AHCL initiation, participants will be instructed to avoid excessive exercise for 48hrs while the algorithm adapts. 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 in communication with participant. Communication can be more often – as per clinical need, and logged.

<u>Visit 4D: Review of AHCL</u> (after 4 weeks from commencement of AHCL, 1 hour)
Face-to-face meeting to upload insulin pump, review CareLink reports and revise settings (CHO ratio and Insulin action time)

Participants will be issued with enough consumables for the study.

Visit 4 (participant randomised to control arm) (10 weeks after randomisation)

<u>Visit 4A: First blinded sensor insertion</u>
<u>Visit 4B: Removal of blinded sensor and second blinded sensor insertion</u>

VISIT 5 (12 weeks after randomisation; 1 hour)

The following data will be collected at the midpoint:
1   Auxological
        Height, Weight, BMI, Blood pressure
2. Diabetes clinical
    a. HbA1c
    b. Total daily dose of insulin (mean of previous 7 days)
    c. Pump upload (for both groups)
    d. Sensor data in the 2 weeks prior to the study visit (in participants on CGM)
    e. Clinical review
3. Psychological assessments
    a. Functional health status: Quality of Life: EQ-5D-3L for 12 to ≤25yrs
    b. Diabetes specific quality of life: PedsQL Child version (<13 yrs), Adolescent version (13 to <18 yrs) and young adult version (18 to ≤25 yrs)
    c. Fear of hypoglycaemia: Hypoglycaemic Fear Survey-II Worry scale: 17 to ≤25yrs. Children's Hypoglycaemia Fear survey 12 to <17 yrs.
    d. Impact and Satisfaction: Diabetes Technology Questionnaire, follow-up version (all ages: only for AHCL)
    e. Diabetes distress: Problem Areas in Diabetes (Paediatric version 12 to <18 yrs, Standard version ≥18 yrs, Parent version)
    f. Hypoglycaemia Awareness: Hypoglycaemia Awareness Scale (Gold Score) (all ages)
    g. Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 (12 to 25 years)
    h. Physical activity: The Active Australia Survey (all ages)
    i. INSPIRE questionnaire (follow-up assessment for those on AHCL)
Participants in the intervention group will be issued with enough consumables for the study

VISIT 6 (23 weeks after randomisation; 30 mins)

<u>Insertion of first blinded CGM</u> (4th generation sensor and transmitter) to collect end-of -study glycaemic data. This constitutes first of the two sensors, each sensor provides data for 7 days. Participants will be instructed to test minimum 4x/day using CONTOUR® NEXT LINK 2.4 glucometer.

VISIT 7 (24 weeks after randomisation; 30 mins)

<u>Insertion of second blinded CGM</u> Participants will return 7 days after sensor insertion 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 transmitter attached.

Medtronic AHCL System Post-Study Patient Questionnaire (Optional)
Phone interview (Optional)

VISIT 8 (26 weeks after randomisation; 2 hours)

The following data will be collected.
1. Auxological
        Height, Weight, BMI, Blood pressure
2. Diabetes clinical
   a. HbA1c

b. Total daily dose of insulin (mean of previous 7 days)
c. Carbohydrate ratios and insulin sensitivity factors
d. Pump upload (for both groups)
e. CGM data from second blinded CGM
f. Sensor data in the 2 weeks prior to the study visit (in participants on CGM)
g. Clinical review

3. Psychological assessments
    1. Functional health status: Quality of Life: EQ-5D-3L for 12 to ≤25yrs
    2. Diabetes specific quality of life: PedsQL Child version (<13 yrs), Adolescent version (13 to<18yrs) and young adult version (18 to ≤25 yrs)
    3. Fear of hypoglycaemia: Hypoglycaemic Fear Survey-II Worry scale: 17 to ≤25yrs. Children's Hypoglycaemia Fear survey 12 to <17 yrs.
    4. Impact and Satisfaction: Diabetes Technology Questionnaire: Follow-up version (all ages only for AHCL)
    5. Diabetes distress: Problem Areas in Diabetes (Paediatric version 12 to <18 yrs, Standard version ≥18yrs, Parent version)
    6. Hypoglycaemia Awareness: Hypoglycaemia Awareness Scale (Gold Score) (all ages)
    7. Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 (12 to 25 years)
    8. Physical activity: The Active Australia Survey (all ages)
    9. INSPIRE questionnaire (follow-up assessment for those on AHCL)

4 Retinal photographs, performed as part of the routine annual screening, will be collected and retained for centralised assessment

5 Biomarkers
12mL of blood and 50mL of urine will be collected in a fasting state.
    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

Extension phase of the study:

Participants will be provided an option to continue the study for another 6 months. This is to ensure that all participants have access to the intervention (AHCL therapy), to collect safety data for 12 months, to ensure that the glycaemic improvement, if any, is sustained and to explore the behavioural patterns that could potentially affect control in the extension phase after novelty of the new intervention weans off.

1) *Group A:* The intervention group will continue to use AHCL therapy. Participants will be issued with enough consumables for the remainder of the study

2) *Group B:* The control group will be offered AHCL therapy (VISIT 9: commencement of AHCL: same as Visit 4)

3) Both groups will have additional visits at Visit 10 (9 months after randomisation) and Visit 11 (1 year after randomisation).

4) A random selection of participants at PCH, Perth will be offered semi-structured interview after V6

Figure 2: Schematic representation of extension of study phase
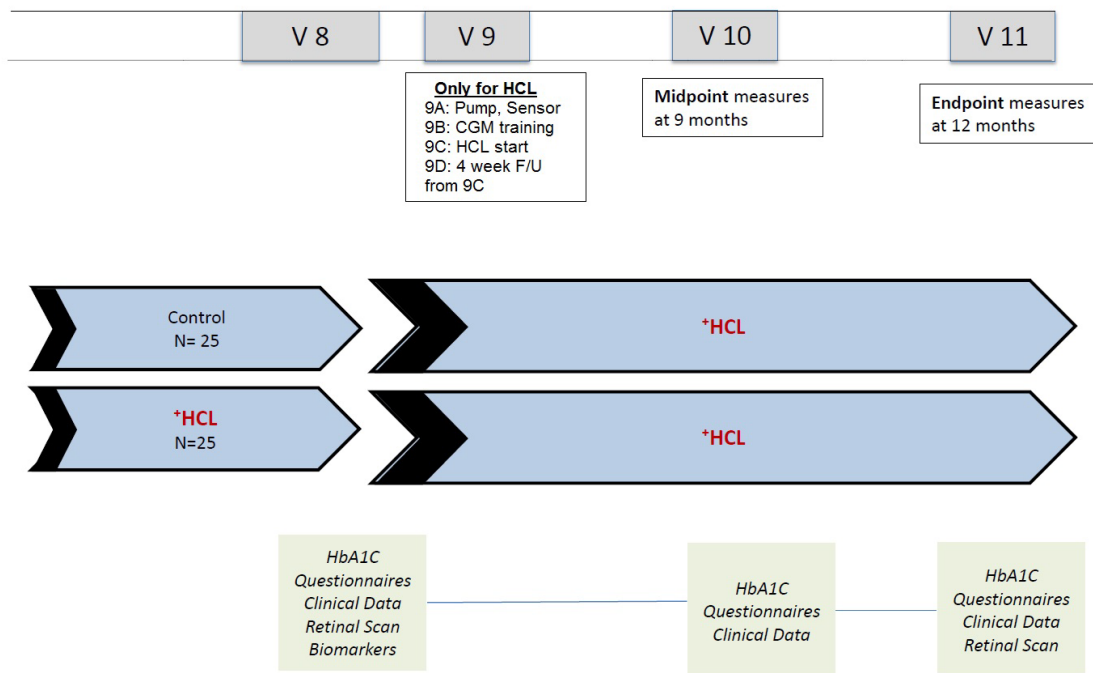
VISIT 9 (Only for participants in the control arm transitioning to AHCL)

CSII to AHCL: Participant 780G 4.0, CGM education and AHCL training.

Visit 9A: Pump training and questionnaires (2 hours)
Participants will be trained on how to use the Medtronic 780G insulin pump. Participants will be provided with Roche Accu-Chek®glucometer along with the glucose strips for the study.

Questionnaires: INSPIRE (baseline), Diabetes Technology Questionnaire (baseline)

Visit 9B: CGM training (2 hours)
They will be instructed on how to link CGM on the Medtronic 780G pump and issued with Guardian Sensor 3 and the Guardian Link 3 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. Sensor naïve individuals will have familiarisation phase of 7 to 10 days to get used to wearing a sensor. Visit 9A and 9B could be combined for participants familiar with sensors.

Visit 9C: Commencement of AHCL (1 hour)
Once CGM data has been established for a minimum of 3 to 7 days, participant returns for face-to-face instruction on AHCL use and initiation of Automode. During this visit, the sensor will be replaced, to demonstrate sensor warm up and AHCL initiation, and provide an opportunity for those unfamiliar with CGM use to practice a sensor change with supervision. Upon AHCL initiation, participants will be instructed to avoid excessive exercise for 48hrs while the algorithm adapts. 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 9D: Review of AHCL (after 4 weeks from commencement of AHCL, 1 hour)
Face-to-face meeting to upload insulin pump, review CareLink reports and revise pump settings (as necessary)

Participants will be issued with enough consumables for the study

VISIT 10 (9 months after randomisation; 1 hour)

The following data will be collected.
1. Auxological
     Height, Weight, BMI, Blood pressure
2. Diabetes clinical
   a. HbA1c
   b. Total daily dose of insulin (mean of previous 7 days)
   c. Carbohydrate ratios and insulin sensitivity factors
   d. Pump upload (for both groups)
   e. Sensor data in the 2 weeks prior to the study visit (in participants on CGM)
   f. Clinical review
3. Psychological assessments
   a. Functional health status: Quality of Life: EQ-5D-3L for 12 to ≤25yrs
   b. Diabetes specific quality of life: PedsQL Child version (<13 yrs), Adolescent version (13 to <18 yrs) and young adult version (18 to ≤25 yrs)
   c. Fear of hypoglycaemia: Hypoglycaemic Fear Survey-II Worry scale: 17 to ≤25yrs. Children's Hypoglycaemia Fear survey 12 to <17 yrs
   d. Impact and Satisfaction: Diabetes Technology Questionnaire, follow-up version (all ages)
   e. Diabetes distress: Problem Areas in Diabetes (Paediatric version 12 to <18 yrs, Standard version ≥18yrs, Parent version)
   f. Hypoglycaemia Awareness: Hypoglycaemia Awareness Scale (Gold Score) (all ages)
   g. Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 (12 to 25 years)
   h. Physical activity: The Active Australia Survey (all ages)
   i. INSPIRE questionnaire

Participants will be issued with enough consumables for the study

VISIT 11 (12 months after randomisation; 2 hours)

The following data will be collected at the end of the study.
1. Auxological
     Height, Weight, BMI, Blood pressure
2. Diabetes clinical
   1. HbA1c
   2. Total daily dose of insulin (mean of previous 7 days)
   3. Carbohydrate ratios and insulin sensitivity factors
   4. Pump upload (for both groups)
   5. Sensor data in the 2 weeks prior to the study visit (in participants on CGM)
3. Psychological assessments
   a. Functional health status: Quality of Life: EQ-5D-3L for 12 to ≤25yrs
   b. Diabetes specific quality of life: PedsQL Child version (<13yrs), Adolescent version (13 to <18 yrs) and young adult version (18 to ≤25 yrs)
   c. Fear of hypoglycaemia: Hypoglycaemic Fear Survey-II Worry scale: 17 to ≤25yrs. Children's Hypoglycaemia Fear survey 12 to <17 yrs.
   d. Impact and Satisfaction: Diabetes Technology Questionnaire, follow-up version (all ages)Diabetes distress: Problem Areas in Diabetes (Paediatric version 12 to <18yrs, Standard version ≥18yrs, Parent version)
   e. Hypoglycaemia Awareness: Hypoglycaemia Awareness Scale (Gold Score) (all ages)
   f. Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 (12 to 25 years)
   g. Physical activity: The Active Australia Survey (all ages)
   h. INSPIRE questionnaire
4. Retinal photographs, performed as part of the routine annual screening, will be collected and retained for centralised assessment
5. Semi-structured interview: A random selection of participants at PCH, Perth will be offered semi-structured interview within 4 weeks of completion of the study.

4.3   Measures taken to minimise/avoid bias, including randomisation and blinding.

Blinding is not possible, in this open label study. Minimisation will be used to allocate participants to study group based on the following balancing factors measured at baseline: age at Visit 1, HbA1c at Visit 1, and study site (MinimPy) (15). Participants will be allocated to the minimisation-preferred group with a probability to 70%. Minimisation is a method of ensuring excellent balance between

groups for known prognostic factors (16). Randomisation will be undertaken by the delegated persons at Perth Children's Hospital.

4.4 Maintenance of any blinding records or randomisation codes and procedures for breaking codes.

As this study is not blinded, the maintenance of breaking codes is not required.

4.5 Method of tracking implantable medical devices (if applicable).

Device serial numbers will be attributed to each study participant and recorded on an excel worksheet as they are issued. At the conclusion of the study, devices will be returned and checked off against the excel worksheet.

4.6 A description of the interventions or investigational product(s). For drug trials information regarding the dosage and dosage regimen, as well as a description of the dosage form, packaging, dispensing and labelling should be included.

The user manuals for 780G system are supplied electronically (they are large, and not appropriate for printing).

4.7 Accountability procedures for the investigational product(s) including the placebo(s) and comparator(s) (if applicable).

The study investigators will be responsible for patient safety during the study. The participants on AHCL will be contacted on a regular basis to monitor progress and help troubleshoot the problems.

4.8 Expected duration of the trial and participant participation, including a description of the sequence and duration of all techniques or assessments to be performed, including follow-up (e.g. interventions, procedures, measurements, observations, laboratory investigations). Provide a schedule of assessments in a table if possible.

The trial is expected to take 2.6 years for recruitment and completion of study visits. For each participant, the expected study duration is 13 months. The schedule of assessments is provided in the table below.

	Screen	| Visits |								| Extension phase: Optional |	
		1	**2**	**3**	**4***	**5**	**6**	**7**	**8**	**9***	**10**	**11**
		Primary phase								Extension phase: Optional		
Length of time of visit (hours)		1-2	0.5	4-6	6	1	0.5	0.5	2	6	1	2
Weeks from Randomisation (+/- 3 weeks window)		-2	-1	0	1 to 4	12	23	24	26	28	36	52
Informed Consent		x										
C-peptide	x											
HbA1c	x	x		x		x			x		x	x
Auxological data		x				x			x		x	x
Diabetes clinical data		x		x		x			x		x	x
bHCG		x										
Insulin pump upload		x		x		x			x		x	x
Carbohydrate Counting				x								
Diabetes education				x								
Blinded sensor		x	x		x		x	x				
Pump training					x					x		
CGM training					x					x		
AHCL commencement					x					x		
Pump/CGM data clinical review				x	x	x			x	x	x	
Psychology measures		x		x	x				x	x	x	x
Retinal Scan				x					x			x
Biomarkers				x					x			
Face-to-face Interview#									x			x
Phone Interview (optional)								x				
Medtronic Questionnaire (optional)				x				x				
		* AHCL: Visit 4 has 4 visits (4A,4B, 4C and 4D); Visit 9 has 4 visits(9A,9B, 9C and 9D); Control: V4 at 10 weeks after randomisation # Random selection of participants at Perth will be offered semi-structured interview at study end (V8 or V11)										

4.9 Criteria for the termination of the trial. Description of the discontinuation criteria for individual participants, parts of the trial and entire trial.

Study participation is voluntary, and participants may withdraw at any time. The DSMB will report to the ethics committees and investigators if stopping the trial is required.

In general, once a participant is randomised, he/she will remain in the study unless the investigator believes it is not safe for the participant to continue. However, the criteria below will be used to determine whether use of the AHCL should be discontinued for a participant.

1. Severe hypoglycaemia (seizure or coma or any episodes requiring third party assistance).
2. Severe diabetic ketoacidosis (venous ph <7.2)
3. Participant pregnancy
4. Non-compliance 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 participant

If AHCL use is stopped according to the above criteria, but the participant 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 participants 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.

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 participants, 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 DKA from Automode use (algorithm-related) in the AHCL group will result in temporarily stopping additional enrolment of participants 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 participants 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 DKA in the AHCL 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 Center will track all participant withdrawals. If the above rule is met (AHCL 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.

4.10 The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered to be source data.

Every participant will be given a unique study number. All data on CRF will be de-identified.

5. Source and Selection of Participants

5.1 **Source of participants** - research population, sample size, source, and sampling frame (if possible, split by site if multicentre trial).

Eligible participants will be identified through the Western Australian Children's Diabetes Database (WACDD) and state specific databases. A generic invite with the information sheet will be sent electronically. Participants will also be identified during their clinic visits. We may also use advertisements, notices, and/or media to recruit participants. 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. Indirect recruitment will also be conducted in these sites with authorised access request: Fiona Stanley Hospital, Sir Charles Gairdner Hospital, and Rockingham General Hospital.

5.2 **Participant inclusion criteria.** Describe appropriate criteria for special risk populations (e.g. women of reproductive age, participants with disease states or organ impairment).

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. Pump therapy for at least 6 months
4. Age 12 to 25 years
5. Recent HbA1c > 8.5% in the last 3 months
6. Mean HbA1c > 8.5% for 6 months
7. Willing to follow study instructions
8. Willing to perform ≥ 3 finger stick blood glucose measurements daily
9. Willing to perform required sensor calibrations
10. Capable of reading and understand instructions in English
11. Living in an area with internet and cellular phone coverage
12. Minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units

5.3 **Participant exclusion criteria.** May include conditions that increase the risk to the participant, that interfere with the participant's ability to give informed consent or interfere with a participant's ability to comply.

1. Participants using closed loop therapy within the past 3 months
2. Severe DKA in the 6 months prior to the screening visit
3. Use of any non-insulin glucose-lowering agent within the past 3 months

4. Commenced CGM in the 3 months prior to the screening visit
5. Pregnancy or planned pregnancy within the study period
6. Uncontrolled coeliac disease (not following a gluten free diet), or other untreated malabsorption
7. Uncontrolled thyroid disease
8. Clinically-significant gastroparesis
9. Poor visual acuity precluding use of the investigational technology
10. Inability or unwillingness to meet protocol requirements
11. Severe or unstable medical or psychological condition which, in the opinion of the treating physician and/or investigator, would compromise the ability to meet protocol requirements

5.4 **Participant withdrawal criteria** (i.e. terminating investigational product/trial treatment) and procedures specifying:

(a) when and how to withdraw participants from the investigational product/trial treatment;
The participant may withdraw from the study at any time. They can do so by contacting the research staff.

(b) the type and timing of the data to be collected for withdrawn participant(s);
As this is an ITT, the data for withdrawn participants will be used for analysis

(c) whether and how participants are to be replaced;
Participants will not be replaced.

(d) the follow-up for participants withdrawn from the investigational product/trial treatment.
The participants will go back on their standard therapy and will be followed up as their regular clinic visits.

6. Treatment of Participants

6.1 **Description and justification for the treatments**, interventions or methods to be utilised (including product name(s), dose(s), dosing schedule(s), route/mode(s) of administration and treatment period(s)) and the follow-up period(s) for participants for each investigational product/trial treatment group/arm of the trial.

The Medtronic advanced hybrid closed loop system compromises the Medtronic MiniMed ™ 670G 4.0 /780G insulin pump containing the closed loop algorithm, a 4th generation glucose sensor and a glucose sensor transmitter. This system is the intervention provided to the participants for 6 months.

Short-acting Insulin is administered subcutaneously via the pump. The pump delivers insulin (microbolus) every 5 minutes (basal insulin) and the amount is dependent on the sensor glucose levels. The system needs the entry of CHO amount by the user at meal times. This HCL system has an advanced closed loop algorithm from the current version being used in two of our research studies (2016087EP and 2016051EP).

6.2 The **medications/treatments permitted** (including rescue medication) and not permitted before and/or during the trial.

For severe hypoglycaemia, intramuscular glucagon can be administered.

For ketosis > 0.6 mmol/l with blood glucose > 15mmol/l, insulin (short-acting) is administered with a pen.

This is taught to every family at the time of diagnosis of T1D and review of their knowledge is established in subsequent clinic follow-ups.

6.3 The **procedures for monitoring participant compliance.**

The study is targeted at patients with poor glycaemic control where adherence to current treatment is suboptimal. Participants randomised to the intervention arm will receive support from the research staff to help them familiarise themselves with the "intervention".

They will also receive assistance to help troubleshoot sensor issues. Participant's pump will be uploaded at each visit and the clinical review at every 3 months will provide an opportunity to engage and encourage the use of the system.

7. Assessment of Efficacy

7.1   Specification of the efficacy parameters.
         Glycaemic control will be measured by HbA1c every 3 months

7.2   The methods and timing for assessing, recording, and analysing efficacy parameters.
         DCA Vantage HbA1c analyser for measuring HbA1c

8. Assessment of Safety

8.1   Summary of **known and potential risks and benefits**, if any, to research participants.

There is a small risk of insulin pump site and glucose insertion site bruising, or skin reaction. However all participants have used insulin pumps and sensors previously. Any patient receiving insulin at any time has the potential to develop hyper or hypoglycaemia. These devices specifically aim to minimise that potential for that risk.

<u>Risks associated with AHCL system in Auto and Manual Mode</u>:
Sensor glucose is populated in the Bolus Wizard automatically by the system when taking a bolus. Sensor glucose is not the same as blood glucose. Sensor performance may occasionally vary from sensor to sensor and in different situations for a sensor, such as on the first day of use.
• Hypoglycaemia or Hyperglycaemia when using sensor glucose values to calculate a meal bolus:
   o If a sensor value is much lower than a blood glucose would be at that time, there is a risk of hyperglycaemia, because the amount of insulin delivered could be smaller
   o If a sensor glucose is much higher than a blood glucose at that time, there is a risk of hypoglycaemia, because the amount of insulin delivered could be larger
   o If participant feels low (but sensor glucose value is not low) or if participant is experiencing severe hypoglycaemia, severe hyperglycaemia or DKA, participant should do a BG check with the meter.

• Hypoglycaemia or Hyperglycaemia when auto correction (auto bolus) is activated:
   o If a sensor glucose is much higher than a blood glucose at that time, there is a risk of hypoglycemia, because the amount of insulin delivered could be larger
   o If participant feels low (but sensor glucose value is not low) and if participant is experiencing severe hypoglycaemia, severe hyperglycaemia or DKA, participant should do a BG check with the meter.

<u>Risks associated with Paracetamol use</u>:
• False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of paracetamol active in the patient's body and may be different for each person.
Note: If participant is using paracetamol or medications containing paracetamol (e.g. cold, pain, fever, and cough medications) while in Auto Mode:
• Participant will be instructed by the study doctor not to use sensor glucose readings to make treatment decisions until participant has stopped using products that contain paracetamol
• Participant should take additional blood glucose meter readings to verify glucose levels.
• Participant should turn off Auto Correction.
• Participant should consider exiting Auto Mode.

8.2   The **safety parameters** and the methods and timing for assessing, recording, and analysing safety parameters. Include a description of emergency procedures if applicable.

This is a cohort of participants with poor glycaemic control and sub-optimal adherence to treatment and safety measures will be put in place.
   a. Participants will be contacted on a weekly basis (or more frequently as required) for at least 4 weeks after commencement of AHCL to review progress.
   b. Participants with high blood/sensor glucose levels will be advised to test for blood ketones.

Participants in the control group will be advised to follow the clinical pathway while participants in the intervention group will be advised to contact the research doctor/diabetes educator.

c. . In the event of device (pump) failure, the participant will be advised to switch to their standard pump therapy and contact the research doctor/diabetes educator.

d. Participants in the intervention group will be informed to contact the research diabetes educator if they experience technical issues with the sensor and/or system

e. Patients are educated regarding awareness of insulin infusion failure (rising blood glucose levels and ketones) and how to manage this (using standard injected subcutaneous insulin, and change insulin infusion set).

f. At each clinic visit, data will be forwarded to the principal investigator. Any admissions to hospital for DKA or severe hypoglycaemia will reported to the principal investigator with 24hrs.

g. Establishment of Data and Safety Monitoring Board (DSMB) to review progress

All serious adverse events are to be recorded and reported to the investigators within 24 hours of notification to lead site and sponsor as well as other regulatory bodies i.e. TGA. All Severe Adverse Events, whether related to the investigational device or not will be reported to the device manufacturer.

8.3 Details of the **Data and Safety Monitoring Board**, or equivalent. *For further information refer to the TGA "Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)" 2000.*

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, DSMB will be established. The board will receive and review information on the progress and accruing data and provide advice on the conduct of the trial to the Investigators. The DSMB will 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.

8.4 The procedures for eliciting reports of and for recording and reporting **adverse events**. Include definitions of adverse events. *For further information on adverse events refer to the TGA "The Australian Clinical Trial Handbook" 2006.*

Adverse Event
Any undesirable clinical occurrence in a participant 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 causally related to the device implantation procedure, the presence of the device, or the performance of the device system.

Severe adverse events
1. Severe Diabetic ketoacidosis (venous ph <7.2)
2. Severe hypoglycaemia (seizure or coma or episodes requiring third party assistance)
3. Results in death, is life-threatening
4. Requires inpatient hospitalization

8.5 The type and duration of the **follow-up** of participants after adverse events.

The follow-up of participants after adverse events will follow standard clinical care pathway of the institution.

9. Data Management, Statistical Analysis and Record Keeping

9.1 Description of the statistical methods to be employed, including timing of any planned interim analysis.

Primary study phase
Data collected and baseline and Visit 8 (i.e. prior to 'extension phase') will be used to assess the effectiveness of AHCL therapy as compared to standard therapy.

The primary analysis will assess differences in time in range (%) with hybrid closed-loop versus standard therapy, measured six months post-randomisation using analysis of covariance (ANCOVA) with adjustment for baseline time in range. Least square means and least square mean differences and their associated 95% confidence intervals will be presented for each treatment group and between groups.

Model residuals will be used to assess model fit. If the residuals indicate poor model fit, the outcome variable will be transformed and the model refitted and evaluated. If poor model fit cannot be addressed, nonparametric analysis will be performed. In the event that residuals are not normally distributed: the Mann–Whitney–Wilcoxon (Wilcoxon Rank-Sum) Test will be employed if raw data are symmetric; if raw data are non-symmetric, bootstrap methods will be used to test the difference between groups.

Continuous secondary outcomes (glycaemic, auxological, clinical, psychosocial) will be analysed using the ANCOVA approach described above.

Secondary analysis for outcomes collected at multiple time points will be conducted using linear mixed models including random effects and various variance-covariance structures to account for non-independence. Akaike information criterion (AIC) will be used to determine the most appropriate model.

No interim analyses are planned apart from the DSMB safety review reported above.

Extension phase
The extension phase will allow device access to all participants taking part in the study and will allow safety data to be collected over a longer period of time. The effects noted during this period are not of primary interest and the approach to analysing extension phase data will be largely exploratory.

We will describe the patterns in primary and secondary outcomes from 6 months to 12 months in Group A (receiving the intervention at both time points) and compare the 6-month post-intervention effect size in Group B to that observed in Group A during the primary study phase.

Primary and secondary outcome scores, paired differences, and their 95% confidence intervals will be presented.

9.2   The number of participants planned to be enrolled (if possible, include number at each site). Document the reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

The power calculation is for a parallel study design with two groups of equal size.

The power calculation is for a parallel study design with two groups of equal size. Based on information in the WA population-based database and current data (de Bock et al, accepted JDST 2018), we expect a between group difference of 1.5% in HbA1c at 6 months with a SD of 1.7% for both groups. With alpha set at 0.05, 22 subjects would be required in each group to have 80% power to detect a difference of 1.5%. It is assumed the total dropout rate will be up to 15%, so we plan to recruit 50 subjects in total.

9.3   The level of significance to be used.
P-values <.05 will be considered statistically significant and 2-sided P-values will be reported.

9.4   Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
Any deviations to the original statistical plan will be reported to relevant ethics committees, governance committees, the Australia New Zealand Clinical Trial Register (ANZCTR), the DSMB and the manuscript.

9.5   The selection of participants to be included in the analyses (e.g. all randomised participants, all dosed participants, all eligible participants, or all evaluable participants).

The primary analysis will take a modified intention-to-treat approach, with all randomised participants who attended at least one visit following randomisation being included in the analysis. A secondary analysis using a 'per-protocol' sample (defined as participants with over 70% adherence to pump and sensor) will also be conducted.

9.6   Information on how data will be managed, including coding for computer analysis and data handling (collection, storage, maintenance, security and archiving). Include details regarding these processes if the data is sent off-site (e.g. encryption). *Clinical trial records should be retained for a minimum of 15 years from the completion of the trial.*

All data will be anonymised and will not be able to be linked back to any individual participant. Data will be stored on secure servers and electronic device capture systems with secure access for study staff only and all data will be stored in an anonymised form that cannot be linked back to the original participant. All data will be stored for 25 years in line with GCP requirements on secure servers. Hard copies of patient notes will be stored in secure filing cabinets at each site and archived in secure facilities' at the end of the trial.

Medtronic CareLink® System:
This system allows the study device to send information over the internet using a telecommunication network (such as a cellular network, wireless network, etc.). The information available from the Medtronic CareLink system is the same information the study team would collect from your device during an in-person office visit. Medtronic will receive participant's coded (deidentified) device data from CareLink®.

Medtronic takes steps to protect the privacy of the health information sent to the Medtronic CareLink Network over the internet. However, Medtronic cannot guarantee the health information is protected against unauthorized interception.

9.7   Procedure for accounting for missing, unused, and spurious (*false*) data.

Multiple imputations will be used to account for missing/spurious data. Analysis using complete case and multiple imputation methods will be presented in the

10. Monitoring / Audit

10.1   Statement that the trial investigators/institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but not limited to, review by external sponsors, Human Research Ethics Committees and institutional governance review bodies.

The trial investigators/institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents

10.2   Description of the procedures for monitoring and auditing. *The clinical trial sponsor may nominate the form of monitoring and auditing and will indicate the times of audit visits.*

The study is monitored by the coordinating principal investigator monthly. The DSMB will have access to the data.

11. Quality Control and Quality Assurance

11.1   Statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.

The trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.

11.2   Quality control & quality assurance measures to ensure quality of data.

All staff will be trained to ensure appropriate data collection in accordance with ICH-GCP guidelines. They will be trained on how to fill out the CRFs to ensure quality of data. Study staffs are experienced diabetes educators and have been involved with research.

The investigator will be monitoring the closed loop system, and will have the back-up of the Medtronic R&D team.

12. Ethics

12.1 Description of ethical considerations related to the trial with particular reference to participant consent (including Participant Information and Consent Forms).

Participants are informed that their consent is voluntary and their participation in the trial or not will not affect their treatment in the clinic. Participants will also be informed that they are unable to keep the investigational devices.

13. Budget, Financing, Indemnity and Insurance

13.1 Budget, financing, indemnity and insurance, if not addressed in a separate agreement.

14. Publication

14.1 Publication and dissemination of trial results (including any limitations), if not addressed in a separate agreement. *In accordance with the Declaration of Helsinki (2008) every clinical trial must be registered in a publicly accessible database before recruitment of the first participant.*

The study will be registered at Australia New Zealand Clinical Trial Register (ANZCTR). Final results will disseminated in a publication and presented at local and international conferences. All participants will be invited to a publicly open research evening hosted annually by the diabetes and endocrinology department where results will be presented

15. References

15.1 A list of articles from the literature pertinent to the evaluation of the trial. Include references that have been cited in the protocol.
1. Craig ME TS, Donaghue KC, Cheung NW, Cameron FJ, Conn J, Jenkins AJ, Silink M, for the Australian Type 1 Diabetes Guidelines Expert Advisory Group. National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults. Australian Government Department of Health and Ageing, Canberra 2011. 2011.
2. Phelan H, Clapin H, Bruns L, Cameron FJ, Cotterill AM, Couper JJ, et al. The Australasian Diabetes Data Network: first national audit of children and adolescents with type 1 diabetes. The Medical journal of Australia. 2017;206(3):121-5.
3. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. Diabetes care. 2004;27(4):955-62.
4. Aagren M, Luo W. Association between glycemic control and short-term healthcare costs among commercially insured diabetes patients in the United States. Journal of medical economics. 2011;14(1):108-14.
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16. Appendices

List all appendices. Including an Investigator's Brochure or Device Manual (if applicable). *All trials involving unregistered drugs must be accompanied by an investigator's brochure which is a compilation of the clinical and non-clinical data available on the experimental products intended for use in the trial. Clinical investigations involving devices should include an Investigator's Brochure or Device Manual.*

16.1 Diabetes Distress Scales

                Problem Areas in Diabetes (paediatric)
                Problem Areas in Diabetes (standard)
                Problem Areas in Diabetes (parent)

16.2 Fear of Hypoglycaemia

                Hypoglycaemia Fear Survey II
                Children's Hypoglycaemia Fear Survey

16.3 General Anxiety

                Generalized Anxiety Disorder-7
                Patient Health Questionnaire-9

16.4 Generic Health Status

                EQ-5D-3L

16.5 Diabetes Specific quality of life

                Peds QL, child, adolescent, young adult

16.6 Treatment Satisfaction

                DTQ

16.7 Hypoglycaemia Awareness

                Gold Question

16.8 Inspire Questionnaire

                Baseline and post assessment (Children, Adolescents and Adults)

16.9 Physical Activity

                The Active Australia Survey

16.10 Medtronic AHCL System

                Background Patient Questionnaire
                Post-Study Patient Questionnaire

16.11 Biomarker Collection Methodology

16.12 Auto-mode take-home points

16.13 Face-to-Face Interview guide

16.14 Phone Interview Guide

Investigator brochure and manuals are uploaded electronically. User guides are too large to be added as Appendices and are uploaded onto RGS instead.

    a)   Feasibility System User Guide Indications and User Safety V1 Jan2019
    b)   User Guide for Minimed 670G 4.0 CGM V1 Jan2019
    c)   User Guide for Minimed 670G 4.0 Insulin Pump V1 Jan2019
    d)   User Guide for Minimed 670G 4.0 SmartGuard Auto Mode V1 Jan2019
    e)   CareLink Participant Uploading Instructions V1 17Feb2020
    f)   Minimed™ 780G System User Guide

16.1 Diabetes Distress Scales

PAID-Paed (12 – <18 years)

PROBLEM AREAS IN DIABETES—PEDIATRIC (PAID-Peds) SURVEY

The following statements describe diabetes-related issues that may or may not be a concern for you. For each item, choose the <u>ONE</u> answer that best describes how much you agree or disagree with that statement.

DURING THE PAST MONTH…	Agree	---->	Neither Agree nor Disagree	---->	Disagree
1. I feel sad a lot when I think about having diabetes.	⓪	①	②	③	④
2. I feel like diabetes has taken over my life.	⓪	①	②	③	④
3. I feel like it is my fault when my blood sugar is out of range.	⓪	①	②	③	④
4. It bothers me to think so much about what I eat.	⓪	①	②	③	④
5. I worry all the time about how diabetes will affect me when I am older.	⓪	①	②	③	④
6. I feel upset when my blood sugar is out of range.	⓪	①	②	③	④
7. I am too tired of having diabetes to take care of it.	⓪	①	②	③	④
8. I feel left out when I can't eat things other teens are eating.	⓪	①	②	③	④
9. I am annoyed when I have to stop what I am doing to check my blood sugar.	⓪	①	②	③	④
10. I am tired of trying to figure out my insulin dose at every meal.	⓪	①	②	③	④
11. I feel embarrassed about having diabetes.	⓪	①	②	③	④
12. My friends and/or family act like the "diabetes police" (for example, always reminding me to eat right, check blood sugars, or take insulin).	⓪	①	②	③	④
13. I am tired of remembering to give insulin shots or to bolus.	⓪	①	②	③	④
14. It seems like no matter how hard I try, my blood sugars are out of control.	⓪	①	②	③	④
15. I feel like I don't fit in with other teens my age because of my diabetes.	⓪	①	②	③	④
16. I am annoyed by having to rotate injection sites or pump infusion sites.	⓪	①	②	③	④
17. I feel angry a lot when I think about having diabetes.	⓪	①	②	③	④
18. My friends and family do not understand what it is like to have diabetes.	⓪	①	②	③	④
19. I worry about going low, especially during physical activities (for example, sports, playing outside, dance class).	⓪	①	②	③	④
20. My parents worry about me and my diabetes too much.	⓪	①	②	③	④

Problem Areas in Diabetes (PAID) © Joslin Diabetes Center 2013

Standard PAID (≥18 years)

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?	☐	☐	☐	☐	☐

Parent PAID

PROBLEM AREAS IN DIABETES—PARENT (PAID-PR) SURVEY REVISED

The following statements describe diabetes-related issues that may or may not be a concern for you. For each item, choose the ONE answer that best describes how much you agree or disagree with that statement.

	Agree				Disagree
1. I feel discouraged with my child's diabetes treatment plan.	⓪	①	②	③	④
2. I feel scared when thinking about my child having/living with diabetes.	⓪	①	②	③	④
3. I have difficulty dealing with school staff (e.g., nurses, teachers, principals).	⓪	①	②	③	④
4. I feel that my child is deprived regarding food and meals.	⓪	①	②	③	④
5. I feel that my child is excluded from activities/events because of his/her diabetes.	⓪	①	②	③	④
6. I feel upset when my child's blood sugars are out of range.	⓪	①	②	③	④
7. I worry about my child having a low blood sugar.	⓪	①	②	③	④
8. I feel angry when I think about my child having/living with diabetes.	⓪	①	②	③	④
9. I feel constantly concerned about what my child eats.	⓪	①	②	③	④
10. I worry about the future and the possibility of serious complications for my child.	⓪	①	②	③	④
11. I feel upset when my child's diabetes management is "off track".	⓪	①	②	③	④
12. I worry that my child will not be taken care of when away from home.	⓪	①	②	③	④
13. I feel like the "diabetes police".	⓪	①	②	③	④
14. I feel that diabetes takes up too much mental and physical energy.	⓪	①	②	③	④
15. I feel alone in managing my child's diabetes.	⓪	①	②	③	④
16. I feel that other family members are not supportive in managing my child's diabetes.	⓪	①	②	③	④
17. I worry whether or not my child will remember to eat his/her snack.	⓪	①	②	③	④
18. I feel "burned out" by the constant effort to manage diabetes.	⓪	①	②	③	④

Problem Areas in Diabetes (PAID) © Joslin Diabetes Center 2011

16.2 Fear 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-<17 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)

1.3 General Anxiety

GAD-7

Over the last two weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Having trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T_____ = ___ + ___ + ___)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the previous 2 weeks, how often have you been bothered by any of the following problems? (Use "✔" to indicate your answer)	Not at all	Several days	More than half of the two week period	Nearly every day
1. Little pleasure or little interest in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Having little energy or feeling tired	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling negative about yourself or that you are a failure or have let your self or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or talking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING ___0___ + _____ + _____ + _____

=Total Score: _____

If you ticked off any of the problems above, how difficult has it been for you to do your work, take care of things at home or get along with other people because of these problems?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

1.4 General Health Status – ED-5D-3L

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	❑ PLEASE TICK
I have some problems in walking around	❑ ONE BOX
I am confined to bed	❑

Personal Care

I have no problems with personal care	❑ PLEASE TICK
I have some problems washing or dressing myself	❑ ONE BOX
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	❑ PLEASE TICK
I have some problems with performing my usual activities	❑ ONE BOX
I am unable to perform my usual activities	❑

Pain / Discomfort

I have no pain or discomfort	❑ PLEASE TICK
I have moderate pain or discomfort	❑ ONE BOX
I have extreme pain or discomfort	❑

Anxiety / Depression

I am not anxious or depressed	❑ PLEASE TICK
I am moderately anxious or depressed	❑ ONE BOX
I am extremely anxious or depressed	❑

2

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

Best imaginable
health state

100

9 0

8 0

7 0

6 0

5 0

4 0

3 0

2 0

1 0

0

Worst imaginable
health state

3

ID#_____
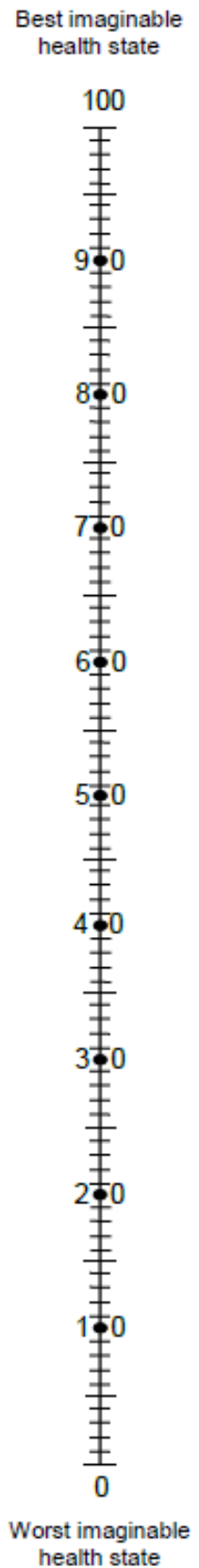
Date:_____

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.

---

*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 3.2 - (8-12) Diabetes
04/09

*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.

---

*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

*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

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

ID#_____

Date:_____

PedsQL^{TM}
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.

---

*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

*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

16.6   Treatment Satisfaction

Diabetes Technology Questionnaire
Part 1: Impact and Satisfaction
<u>Baseline Version</u>

Thank you for giving us your time and effort in taking part in this study. Your opinions about using diabetes technology are very valuable to us and we hope that you can now help us learn how this has affected your daily life with diabetes. Below you will see some statements about different kinds of diabetes treatments that include using different diabetes devices such as a blood glucose meter, insulin pump, continuous glucose monitor or closed loop insulin delivery system.

Please tick the box below that lists the diabetes devices you are using now as part of treatment. If you aren't sure, ask the diabetes nurse to help you.

☐ Glucose Meter(s) and daily use of an insulin pump

☐ Glucose Meter(s) and a Continuous Glucose Monitor (Medtronic, Dexcom or Libre) and daily use of an insulin pump

For those just entering the study: Now we'd like to ask you some questions about the treatment approach that you selected above. We've listed below some parts of living with diabetes that might be made better or worse by your use of diabetes devices. For each of these, please circle the number that best tells how much of a problem it is now.

<u>Is this a problem now?</u>

	Very Much		Just A Little		Not At All
1. Worry or fear about high blood sugar	1	2	3	4	5
2. Effort to keep low blood sugar from happening	1	2	3	4	5
3. Worry or fear about low blood sugar during sleep	1	2	3	4	5
4. Feeling different from others	1	2	3	4	5
5. Amount of time spent thinking about diabetes	1	2	3	4	5
6. Not knowing how eating affects blood sugar	1	2	3	4	5
7. Amount of time and effort needed for diabetes from my family or me	1	2	3	4	5
8. Worry or fear about long term health	1	2	3	4	5

<center>Is this a problem now?</center>

	Very Much		Just A Little		Not At All
9. Worry or fear about daytime low blood sugar	1	2	3	4	5
10. Effort to keep high blood sugar from happening	1	2	3	4	5
11. Pain or discomfort from finger sticks or monitors	1	2	3	4	5
12. Pain or discomfort from insulin injections or pump sets	1	2	3	4	5
13. Family arguments or worries about diabetes	1	2	3	4	5
14. Trouble sleeping well	1	2	3	4	5
15. Strictness of the meal plan	1	2	3	4	5
16. Coping with work or school along with diabetes	1	2	3	4	5
17. Taking part in sports, exercise or playing despite diabetes	1	2	3	4	5
18. Knowing how much insulin to take	1	2	3	4	5
19. Keeping up with friends or peers who don't have diabetes	1	2	3	4	5
20. Reacting to all of the blood sugar results that I get	1	2	3	4	5
21. Dealing with others who ask about diabetes	1	2	3	4	5
22. My amount of responsibility for taking care of diabetes	1	2	3	4	5
23. Being sure that pre-meal insulin covers the amount of carbohydrates eaten	1	2	3	4	5
24. Getting the right amount of insulin when meals are skipped or delayed	1	2	3	4	5
25. Reacting to all of the alarms from diabetes devices	1	2	3	4	5

	Very Much		Just A Little		Not At All
26. Getting the right amount of insulin on sick days.	1	2	3	4	5
27. Feeling that diabetes devices run my life	1	2	3	4	5
28. Getting the right amount of insulin after exercising more than usual	1	2	3	4	5
29. Coping with carrying and using several devices	1	2	3	4	5
30. Looking different because of diabetes and using devices	1	2	3	4	5

Diabetes Technology Questionnaire
Part 1: Impact and Satisfaction
Follow-Up Version

Thank you for giving us your time and effort in taking part in this study. Your opinions about using diabetes technology are very valuable to us and we hope that you can now help us learn how this has affected your daily life with diabetes. Below you will see some statements about different kinds of diabetes treatments that include using different diabetes devices such as a blood glucose meter, insulin pump, continuous glucose monitor or closed loop insulin delivery system.

Please tick the box below that lists the diabetes devices you are using now as part of treatment. If you aren't sure, ask the diabetes nurse to help you.

    ❑ Glucose Meter(s) and daily use of an insulin pump

    ❑ Glucose Meter(s) and a Continuous Glucose Monitor (Medtronic, Dexcom or Libre) and daily use of an insulin pump

For those completing a follow-up study visit: Now we'd like to ask you some questions about the treatment approach that you selected above. We've listed below some parts of living with diabetes that might be made better or worse by your use of diabetes devices. For each of these, please circle the number that best tells how much of a problem it is now and then circle the number that best tells how it has changed for you compared to the treatment received before you entered this study.

	Is this a problem now?					How has it changed compared to your treatment before the study?				
	Very Much		Just A Little		Not At All	Much Worse	A Little Worse	Same	A Little Better	Much Better
1. Worry or fear about high blood sugar	1	2	3	4	5	1	2	3	4	5
2. Effort to keep low blood sugar from happening	1	2	3	4	5	1	2	3	4	5
3. Worry or fear about low blood sugar during sleep	1	2	3	4	5	1	2	3	4	5
4. Feeling different from others	1	2	3	4	5	1	2	3	4	5
5. Amount of time spent thinking about diabetes	1	2	3	4	5	1	2	3	4	5
6. Not knowing how eating affects blood sugar	1	2	3	4	5	1	2	3	4	5
7. Amount of time and effort needed for diabetes from my family or me	1	2	3	4	5	1	2	3	4	5

	Is this a problem now?					How has it changed compared to your treatment before the study?				
	Very Much		Just A Little		Not At All	Much Worse	A Little Worse	Same	A Little Better	Much Better
8. Worry or fear about long term health	1	2	3	4	5	1	2	3	4	5
9. Worry or fear about daytime low blood sugar	1	2	3	4	5	1	2	3	4	5
10. Effort to keep high blood sugar from happening	1	2	3	4	5	1	2	3	4	5
11. Pain or discomfort from finger sticks or monitors	1	2	3	4	5	1	2	3	4	5
12. Pain or discomfort from insulin injections or pump sets	1	2	3	4	5	1	2	3	4	5
13. Family arguments or worries about diabetes	1	2	3	4	5	1	2	3	4	5
14. Trouble sleeping well	1	2	3	4	5	1	2	3	4	5
15. Strictness of the meal plan	1	2	3	4	5	1	2	3	4	5
16. Coping with work or school along with diabetes	1	2	3	4	5	1	2	3	4	5
17. Taking part in sports, exercise or playing despite diabetes	1	2	3	4	5	1	2	3	4	5
18. Knowing how much insulin to take	1	2	3	4	5	1	2	3	4	5
19. Keeping up with friends or peers who don't have diabetes	1	2	3	4	5	1	2	3	4	5
20. Reacting to all of the blood sugar results that I get	1	2	3	4	5	1	2	3	4	5
21. Dealing with others who ask about diabetes	1	2	3	4	5	1	2	3	4	5
22. My amount of responsibility for taking care of diabetes	1	2	3	4	5	1	2	3	4	5
23. Being sure that pre-meal insulin covers the amount of carbohydrates eaten	1	2	3	4	5	1	2	3	4	5
24. Getting the right amount of insulin when meals are skipped or delayed	1	2	3	4	5	1	2	3	4	5

	Is this a problem now?					How has it changed compared to your treatment before the study?				
	Very Much		Just A Little		Not At All	Much Worse	A Little Worse	Same	A Little Better	Much Better
25. Reacting to all of the alarms from diabetes devices	1	2	3	4	5	1	2	3	4	5
26. Getting the right amount of insulin on sick days.	1	2	3	4	5	1	2	3	4	5
27. Feeling that diabetes devices run my life	1	2	3	4	5	1	2	3	4	5
28. Getting the right amount of insulin after exercising more than usual	1	2	3	4	5	1	2	3	4	5
29. Coping with carrying and using several devices	1	2	3	4	5	1	2	3	4	5
30. Looking different because of diabetes and using devices	1	2	3	4	5	1	2	3	4	5

16.7 Impaired 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

16.8 INSPIRE Questionnaire

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 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 (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 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.

5.9   The Active Australia Survey

The questions below are about any physical activities that you may have done in the <u>last week</u>:

1. In the last week, how many times have you walked continuously, for at least 10 minutes, for recreation, exercise or to get to or from places?

    ☐ None ☐ Once ☐ Twice ☐ 3 times ☐ 4 times ☐ 5 times ☐ 6 or more times

2. What do you estimate was the total time that you spent walking in this way in the last week?

    ☐ Hours ☐ Minutes

3. In the last week, how many times did you do any vigorous physical activities, which made you breathe harder or puff and pant (e.g. jogging, cycling, aerobics, competitive tennis)?

    ☐ None ☐ Once ☐ Twice ☐ 3 times ☐ 4 times ☐ 5 times ☐ 6 or more times

4. What do you estimate was the total time that you spent doing vigorous physical activities in the last week (e.g. jogging, cycling, aerobics, competitive tennis)?

    ☐ Hours ☐ Minutes

5. In the last week, how many times did you do any other more moderate physical activities that you have not already mentioned (e.g. gentle swimming, social tennis, golf)?

    ☐ None ☐ Once ☐ Twice ☐ 3 times ☐ 4 times ☐ 5 times ☐ 6 or more times

6. What do you estimate was the total time that you spent doing these activities in the last week (e.g. gentle swimming, social tennis, golf)?

    ☐ Hours ☐ Minutes

To following questions are for participants in intervention arm only at 3, 6, 9, and 12 months post - randomisation:

	Very much		Just a little		Not at all	N/A
1. Has Auto Mode helped you to be more confident in being physically active?	1	2	3	4	5	0
2. Has Auto Mode helped increase your exercise duration/activity?	1	2	3	4	5	0
3. Has Auto Mode helped decrease your fear of overnight lows following exercise?	1	2	3	4	5	0

This survey has been adapted from the Active Australia Survey developed and nationally implemented in Australia in 1997.

Australian Institute of Health and Welfare (AIHW) 2003. The Active Australia Survey: a guide and manual for implementation, analysis and reporting. Canberra: AIHW.

5.10   Medtronic Advanced Hybrid Closed Loop System Questionnaires

5.11

MARKET RESEARCH SURVEY

Medtronic

Advanced Hybrid Closed Loop System Background Patient Questionnaire

Patient ID:

Study ID:

Date:

Verified by (Site Employee):

Note: throughout this survey, we are referring to your current study device Medtronic MiniMed insulin pump and sensor as the "Advanced Hybrid Closed Loop" system.

Approval/Respondent Qualification

[Age] Are you 18 years of age or older?

☐   Yes

☐   No

If you are under 18 years of age, do you have the permission of your parent or guardian to complete this survey?

☐   Yes

☐   No (You must have permission in order to continue)

Are you the individual who participated in the Advanced Hybrid Closed Loop Clinical Study, or a care partner?

☐   I am the actual participant

☐   I am a care partner of an individual under the age of 18 (who is participating in the study)

☐   I am a care partner of another adult (who is participating in the study)

If a caregiver, from this point forward, please answer the questions on behalf of the individual who will actually be using the Advanced Hybrid Closed Loop system.

Section 1: Background

1) In what year were you diagnosed with diabetes? _____

2) In what year did you start using an insulin pump (if applicable)? _____

Section 2: Importance Ratings

3) In general, how important are the following attributes if you were considering switching to new technology to manage your diabetes (whether from Medtronic or another manufacturer)?

		Extremely Important	Very Important	Moderately Important	Slightly Important	Not Important	No Opinion
		5	4	3	2	1	0
1	Improving blood glucose (BG) time-in-range	O	O	O	O	O	O
2	Improving average glucose values	O	O	O	O	O	O
3	Reducing lows at night	O	O	O	O	O	O
4	Reducing lows during the day	O	O	O	O	O	O
5	Reducing lows associated with exercise or sports	O	O	O	O	O	O

		Extremely Important	Very Important	Moderately Important	Slightly Important	Not Important	No Opinion
		5	4	3	2	1	0
6	Reducing highs after meals	O	O	O	O	O	O
7	Amount of time to come down from a high	O	O	O	O	O	O
8	Amount of effort to come down from a high	O	O	O	O	O	O

		Extremely Important	Very Important	Moderately Important	Slightly Important	Not Important	No Opinion
		5	4	3	2	1	0
9	Not having to carb count	O	O	O	O	O	O
10	Not having to bolus for meals	O	O	O	O	O	O
11	Less BGs per day	O	O	O	O	O	O
12	Less alarm/alerts per day	O	O	O	O	O	O
13	Reducing day-to-day effort managing diabetes	O	O	O	O	O	O
14	Reducing mental effort managing diabetes (how much one needs to think about it)	O	O	O	O	O	O
15	Ease of use of the system (pump & sensor)	O	O	O	O	O	O
16	Ease of learning how to use the system	O	O	O	O	O	O

Section 3: Prior Therapy

4) Which of the following insulin pumps did you use previously?

(If you have used several, check the one that you used 'most recently' prior to Hybrid Closed Loop System clinical study)

- ☐ Never used an insulin pump
- ☐ MiniMed® 670G system (Medtronic)
- ☐ MiniMed® 530G System (Medtronic)
- ☐ MiniMed® Paradigm Revel™ 523/723 System (Medtronic)
- ☐ MiniMed® 640G System (Medtronic)
- ☐ MiniMed® Veo™ System (Medtronic)
- ☐ Tandem Basal-IQ
- ☐ Tandem t:slim®
- ☐ Tandem t:flex®
- ☐ ACCU-CHEK® Spirit (Roche)
- ☐ ACCU-CHEK® Spirit Combo (Roche)
- ☐ Animas® Vibe® System (Animas)
- ☐ OneTouch® Ping™ (Animas)
- ☐ OmniPod® (Insulet)
- ☐ Other (Please specify_____)
- ☐ Can't recall specific pump/brand/model

5) How satisfied were you with your previous insulin pump system, prior to using the Advanced Hybrid Closed Loop System?

Extremely satisfied	Very satisfied	Satisfied	Somewhat satisfied	Not satisfied	Not Sure
5	4	3	2	1	0
O	O	O	O	O	O

6) Prior to the Advanced Hybrid Closed Loop clinical trial, had you previously used Continuous Glucose Monitoring (CGM)?

- ☐ Yes
- ☐ No
- ☐ Not sure

7) In what year did you start using a CGM (Please estimate if cannot remember exactly)? _____
(Skip if never used CGM before)

  a) Which CGM device did you use previously (prior to using Advanced Hybrid Closed Loop system)? (Skip if never used CGM before)
  - ☐ Medtronic Enlite® Glucose Sensor
  - ☐ Medtronic Guardian Sensor 3 Sensor
  - ☐ Abbott FreeStyle® Libre (Abbott)
  - ☐ Dexcom G4 Platinum
  - ☐ Dexcom G5 Mobile CGM System
  - ☐ Dexcom G6 Mobile CGM System
  - ☐ Other CGM product (Please specify: _____)
  - ☐ I can't recall

b) Prior to the Advanced Hybrid Closed Loop system, how frequently did you wear the CGM sensor? (Skip if never used CGM before)

- ☐ Every day
- ☐ Nearly every day
- ☐ A few weeks per month
- ☐ About one week per month
- ☐ About 2-4 times a year
- ☐ Less than once a year
- ☐ I don't recall

8) How satisfied were you with your previous CGM, prior to using the Advanced Hybrid Closed Loop System?

Extremely satisfied	Very satisfied	Satisfied	Somewhat satisfied	Not satisfied	Not Sure
5	4	3	2	1	0
O	O	O	O	O	O

9) How would you rate your ability to manage the following on your previous system?

		Excellent	Very Good	Good	Fair	Poor	No Opinion
		5	4	3	2	1	0
1	Reducing lows at night	O	O	O	O	O	O
2	Reducing lows during the day	O	O	O	O	O	O
3	Reducing highs after meals	O	O	O	O	O	O
4	Reduce the effort to carb count	O	O	O	O	O	O
5	Reduce the effort to bolus for my meals	O	O	O	O	O	O
6	Reducing day-to-day effort managing diabetes	O	O	O	O	O	O
7	Reducing mental effort managing diabetes (how much one needs to think about it)	O	O	O	O	O	O
8	Improving blood glucose (blood sugar) time-in-range	O	O	O	O	O	O
9	Ease of use of the system	O	O	O	O	O	O
10	Ease of learning how to use the system	O	O	O	O	O	O

Section 4: Advanced Hybrid Closed Loop system Expectations

10) Once you start using the Advanced Hybrid Closed Loop system, in which of the following areas are you expecting to see improvement? Please rank your top 10 improvements from 1 being the feature that you would like to see the most improvement, 2 being second most improvement, etc.

- ☐ Less day-to-day effort managing my diabetes
- ☐ Better A1C
- ☐ Not having to fingerstick
- ☐ Fewer lows
- ☐ Less amount of time to come down from a high
- ☐ Less effort to come down from a high
- ☐ Not having to carb count
- ☐ More time in range
- ☐ No need to bolus for meals
- ☐ No need to correct my high glucose values
- ☐ Ability to control my pump using my phone
- ☐ Other: _____

Section 5: Profiling, & Demographics

11) Approximately what range was most recent HBA1c result?
- ☐ [12] 5.0 or lower
- ☐ [11] 5.1 to 5.5
- ☐ [10] 5.6 to 6.0
- ☐ [9] 6.1 to 6.5
- ☐ [8] 6.6 to 7.0
- ☐ [7] 7.1 to 7.5
- ☐ [6] 7.6 to 8.0
- ☐ [5] 8.1 to 8.5
- ☐ [4] 8.6 to 9.0
- ☐ [3] 9.1 to 9.5
- ☐ [2] 9.6 to 10.0
- ☐ [1] Greater than 10.0
- ☐ [0] Not sure

12) How satisfied are you with your current HbA1C results?
- ☐ [5] Extremely Satisfied
- ☐ [4] Very Satisfied
- ☐ [3] Somewhat Satisfied
- ☐ [2] Not Very Satisfied
- ☐ [1] Not at all Satisfied
- ☐ [0] Not sure

13) How many times do you test your blood glucose in a single day? _____ [RANGE: 1-20]

14) Is your carbohydrate intake tracked on a regular basis?
- ☐ [2] Yes, very regularly
- ☐ [1] Yes, although not necessarily regularly
- ☐ [0] No

    a) In your opinion, how well are you able to calculate your carbohydrate intake?
- ☐ [5] Extremely Well
- ☐ [4] Very Well
- ☐ [3] Somewhat Well
- ☐ [2] Not Very Well
- ☐ [1] Not at all Well
- ☐ [0] I do not count carbohydrates

    b) In your opinion, how challenging is it to calculate your carbohydrate intake?
- ☐ [4] Very challenging
- ☐ [3] Somewhat challenging
- ☐ [2] Not challenging
- ☐ [1] Not at all challenging
- ☐ [0] Not sure

15) On average how would you describe your meal bolus behavior?
   - ☐ [3] I only bolus for meals if it is convenient to do so
   - ☐ [2] I usually bolus after meals
   - ☐ [1] I usually bolus during meals
   - ☐ [0] I usually bolus before meals

16) What is your birth YEAR? _____

17) What is your gender?
   - ☐ Female
   - ☐ Male

18) Have you participated in prior diabetes clinical trials?
   - ☐ Yes
   - ☐ No
   - a) When did you last participate in a diabetes clinical trial? (Skip this question if never participated in a clinical study)
     - ☐ [3] Within the past 6 months
     - ☐ [2] About 7-12 months ago
     - ☐ [1] About 1-2 years ago
     - ☐ [0] Greater than 3 years ago

MARKET RESEARCH SURVEY

Medtronic

Advanced Hybrid Closed Loop System Post Study Patient Questionnaire

Patient ID:

Study ID:

Date:

Verified by (Site Employee):

Thank you for taking the time to complete this questionnaire. Your answers are valuable to us. Your answers are confidential. There is no right or wrong answers. Please take your time when answering the questions. The questionnaire should take about 20 minutes to complete.

Note: throughout this survey, we are referring to your current study device Medtronic MiniMed insulin pump and sensor as the "Advanced Hybrid Closed Loop" or "AHCL" system.

Approval/Respondent Qualification

[Age] Are you 18 years of age or older?
- ☐ Yes
- ☐ No

If you are under 18 years of age, do you have the permission of your parent or guardian to complete this survey?
- ☐ Yes
- ☐ No (You must have permission in order to continue)

Are you the individual who participated in the Advanced Hybrid Closed Loop Clinical Study, or a care partner?
- ☐ I am the actual participant
- ☐ I am a care partner of an individual under the age of 18 (who is participating in the study)
- ☐ I am a care partner of another adult (who is participating in the study)

If a caregiver, from this point forward, please answer the questions on behalf of the individual who will actually be using the Advanced Hybrid Closed Loop system.

1. Considering your experience with the <u>overall</u> AHCL System, how likely are you to <u>recommend it to others</u>?

Definitely would recommend it	☐
Probably would recommend it	☐
Might or might not recommend it	☐
Probably would not recommend it	☐
Definitely would not recommend it	☐

2. How would you rate the AHCL System for the following categories? Please indicate below.

		1 Not Sure	2 Poor	3 Fair	4 Good	5 Very Good	6 Excellent
1.	Overall rating of the Pump	O	O	O	O	O	O
2.	Overall rating of the sensor	O	O	O	O	O	O
3.	Overall control of low blood glucose	O	O	O	O	O	O
4.	Overall nighttime control of blood glucose	O	O	O	O	O	O
5.	Maximizing time spent in control	O	O	O	O	O	O
6.	Overall control of glucose levels	O	O	O	O	O	O
7.	Reducing lows caused by physical activities	O	O	O	O	O	O
8.	Overall control of blood glucose levels after a meal	O	O	O	O	O	O
9.	Overall control of high glucose levels after not bolusing for meals	O	O	O	O	O	O
10.	Overall control of high blood glucose	O	O	O	O	O	O
11.	Overall ease of use of the system	O	O	O	O	O	O
12.	Ease of use of the pump	O	O	O	O	O	O
13.	Ease of use of the sensor	O	O	O	O	O	O
14.	Overall helpfulness of the alarms	O	O	O	O	O	O

Please <u>compare the AHCL system to your previous therapy system.</u>

3. Considering everything about the AHCL system, which of the following phrases <u>best describes</u> how you feel about it?

The best therapy system I have ever used or tried	☐
Slightly better than any other therapy system I have ever used or tried	☐
About the same as any other therapy system I have ever used or tried	☐
Slightly worse than any other therapy system I have ever used or tried	☐
The worst therapy system I have ever used or tried	☐

4. Considering everything about the AHCL system, which of the following phrases <u>best describes</u> how you feel about it <u>in comparison with your previous therapy system</u>?

Much better than my previous therapy system	☐
Somewhat better than my previous therapy system	☐
About the same as my previous therapy system	☐
Somewhat worse than my previous therapy system	☐
Much worse than my previous therapy system	☐

5. Comparing the AHCL system to your previous therapy system, __which would you prefer__ for the following characteristics?

		1 Prefer AHCL SYSTEM	2 Prefer Previous Therapy System	3 Prefer Both Equally	4 Prefer Neither
1.	Overall performance	O	O	O	O
2.	Overall control of blood glucose levels	O	O	O	O
3.	Maximize time spent in control	O	O	O	O
4.	Control of low blood glucose	O	O	O	O
5.	Control of high blood glucose	O	O	O	O
6.	Ease of use	O	O	O	O
7.	Ease of adjusting insulin therapy	O	O	O	O
8.	Helping to meet my glucose targets (therapy goals?)	O	O	O	O
9.	Effort spent managing my diabetes	O	O	O	O
10	Time spent thinking or worrying about my diabetes	O	O	O	O
11	Freedom with my food choices	O	O	O	O
12	Effort around mealtime	O	O	O	O
13	Effort of carb counting	O	O	O	O

6. Please indicate __how much you AGREE or DISAGREE__ with each of the following statements about the overall AHCL system?

		1 Strongly Disagree	2 Slightly Disagree	3 Neither Agree Nor Disagree	4 Slightly Agree	5 Strongly Agree
1.	Gives me peace of mind	O	O	O	O	O
2.	Helps me engage in my favorite hobbies	O	O	O	O	O
3.	Helps my overall physical well being	O	O	O	O	O
4.	Gives me confidence in my diabetes management	O	O	O	O	O
5.	let's me achieve better control with less effort	O	O	O	O	O
6.	Lets me put in less effort in checking blood glucose levels and calibrating sensors	O	O	O	O	O
7.	Lets me put in less effort in carb counting	O	O	O	O	O
8.	Lets me put in less effort in treating highs	O	O	O	O	O
9.	Helps me lower my A1C	O	O	O	O	O
10.	Helps me and my family worry less	O	O	O	O	O

		1 Strongly Disagree	2 Slightly Disagree	3 Neither Agree Nor Disagree	4 Slightly Agree	5 Strongly Agree
11.	Makes me feel more rested in the morning and with more energy for the whole day	O	O	O	O	O
12.	It helps me feel calm and relaxed	O	O	O	O	O
13.	Improves overall quality of life	O	O	O	O	O
14.	Helps me spend more time in range (time between 3.9mmol/L and 10mmol/L)	O	O	O	O	O
15.	Helps make meal time easier	O	O	O	O	O
16.	I worry less about what I eat	O	O	O	O	O
17.	Helps me think less about my diabetes in social setting	O	O	O	O	O
18.	Helps me sleep better at night	O	O	O	O	O
19.	Lets me put in less effort in managing my diabetes	O	O	O	O	O
20.	Helps make mealtime less stressful	O	O	O	O	O
21.	Helps me feel less restricted around meals	O	O	O	O	O
22.	Gives me freedom with my food choices	O	O	O	O	O
23.	I trust the SmartGuard (Auto Mode) technology	O	O	O	O	O

7. Please indicate how much you AGREE or DISAGREE with the following statements regarding your experience with the AHCL system.

		1 Strongly Disagree	2 Slightly Disagree	3 Neither Agree Nor Disagree	4 Slightly Agree	5 Strongly Agree
1.	I think that I would like to use this system frequently	O	O	O	O	O
2.	I found the system unnecessarily complex	O	O	O	O	O
3.	I thought the system was easy to use	O	O	O	O	O
4.	I think that I would need the support of a technical person to be able to use this system	O	O	O	O	O
5.	I found the various functions in this system were well integrated	O	O	O	O	O
6.	I thought there was too much inconsistency in this system	O	O	O	O	O
7.	I would imagine that most people would learn to use this system very quickly	O	O	O	O	O
8.	I found the system very cumbersome to use	O	O	O	O	O
9.	I felt very confident using the system	O	O	O	O	O
10.	I needed to learn a lot of things before I could get going with this system	O	O	O	O	O
11.	The amount of time spent learning to use the system was reasonable	O	O	O	O	O

8. Please indicate how much you AGREE or DISAGREE with the following statements regarding your experience with not having bolusing for meal while using the AHCL system.

		1 Strongly Disagree	2 Slightly Disagree	3 Neither Agree Nor Disagree	4 Slightly Agree	5 Strongly Agree
1.	The system helps me avoid highs if I forget to dose for a meal	O	O	O	O	O
2.	The system protects me if I forget to dose for a meal	O	O	O	O	O
3.	I feel like I can skip bolusing for snacks and the system still takes care of my diabetes	O	O	O	O	O
4.	I feel like I can skip bolusing for light meals (<40g carb) and the system still takes care of my diabetes	O	O	O	O	O
5.	I feel like I can skip bolusing for all meals and the system still takes care of my diabetes	O	O	O	O	O

End of Survey – Thank you for your participation!

16.11 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)

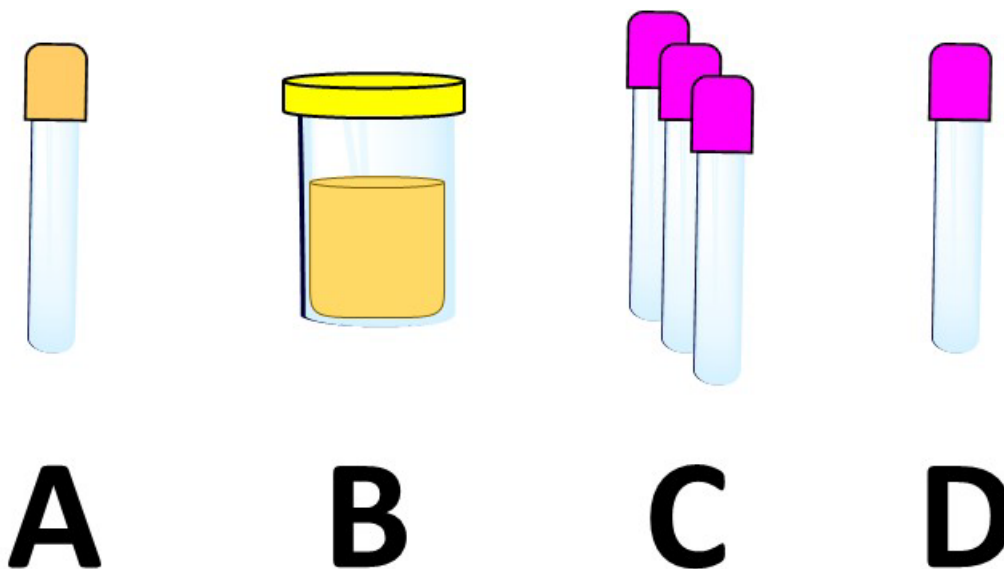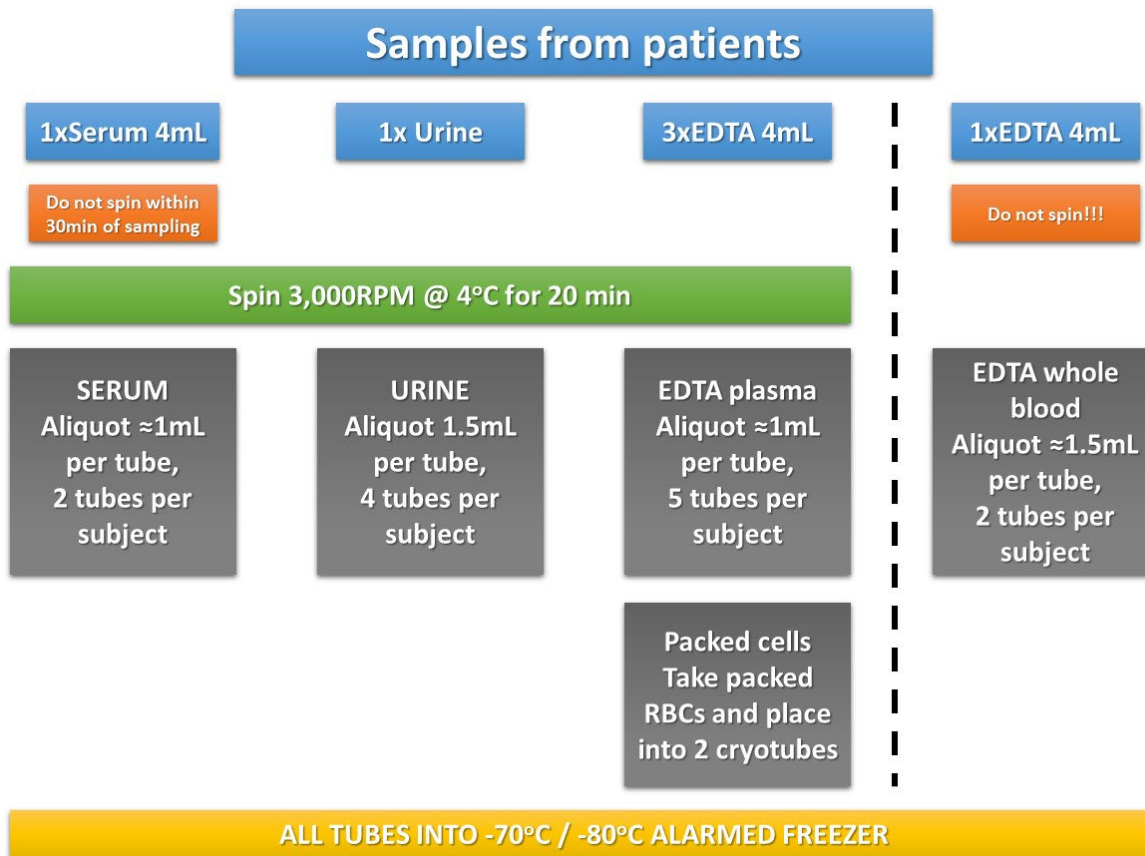Collection tubes are assumed to be BD plastic vacutainers with draw volume of 4mL.

The biomarker samples below are to be collected at V3 and V6.
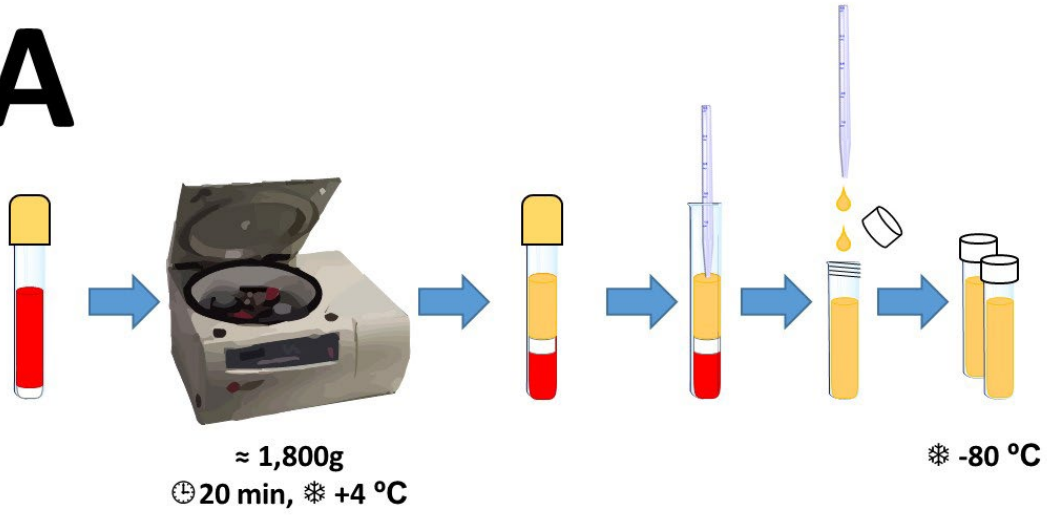K2EDTA BD catalog number: 367839 (lavender)
Serum BD catalog number: 367954 (gold) SST (serum separator tube)

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
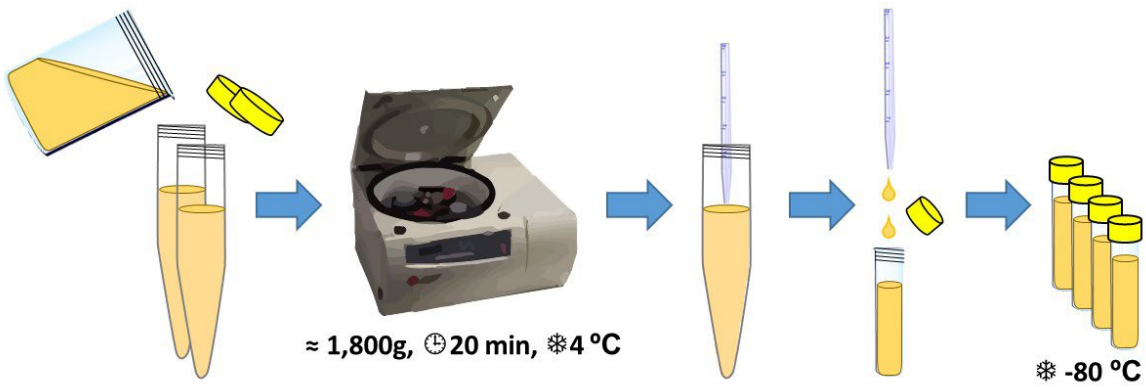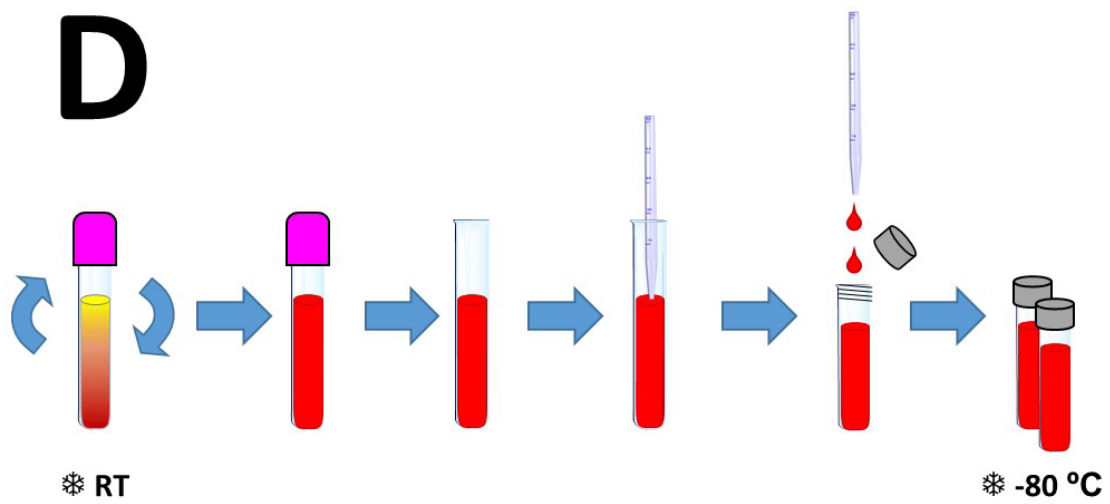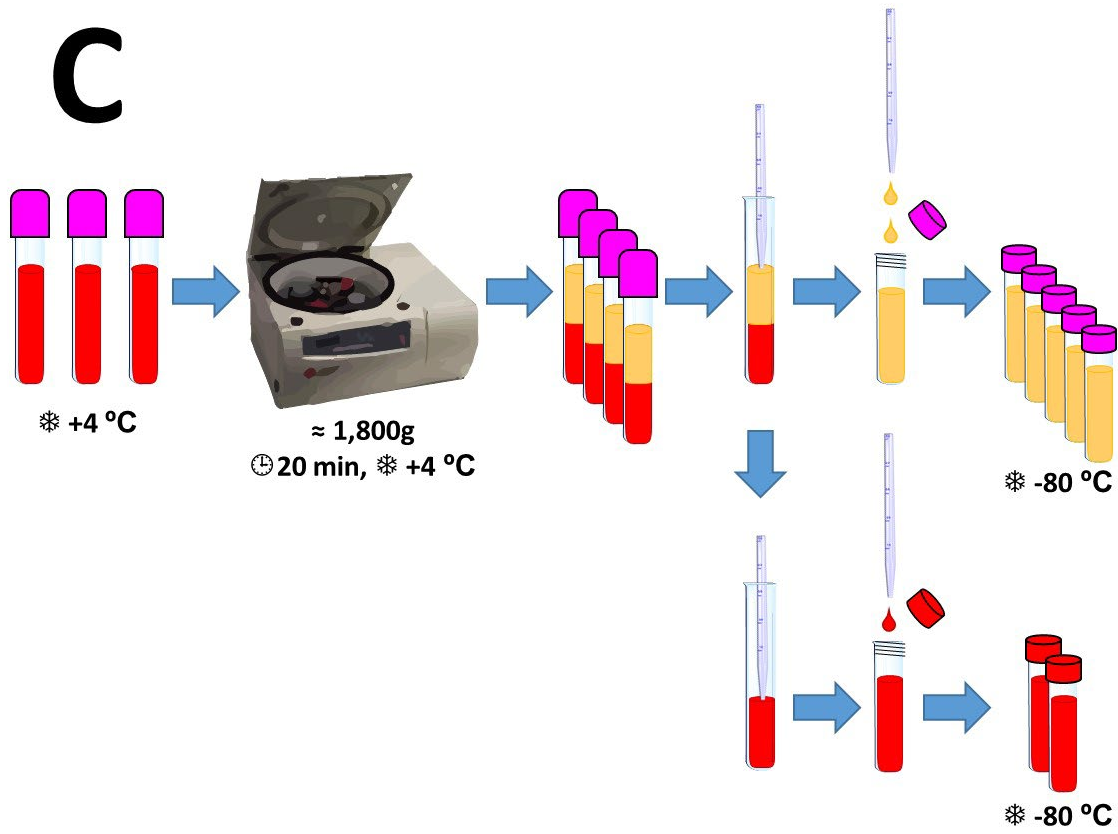
<h1 style="text-align:center">16.12 Auto-mode take-home points</h1>

- Be prepared to be patient when troubleshooting and take time to learn about and trust the system

- Remember to enter meter BG, carbs and bolus *before* meals

- <u>Upload your 670 pump every week for first four weeks, and then as requested by study staff</u>
  – It is important that we are able to review the settings in your pump

- <u>Regular BG calibrations are important</u> - remember to check meter blood glucose (BG) and calibrate sensor at least twice a day and as required by the system

- **<u>Calibrations:</u>**
  - initial calibration – 2 hours after warm-up
  - needs second calibration within six hours of initial calibration
  - calibrate at least twice a day and as required by the system
  - If more than 12 hours between calibrations – will exit Auto mode

- Calibrate and look for 'Blue Shield' before bed and upon waking

- The main reason for Auto-mode changing to manual mode is generally sensor issues

- **Suspend before disconnecting**, to ensure accurate total daily dose (TDD) of insulin. To avoid lost sensor signal alert, keep pump nearby if you disconnect for 30 minutes or longer

- Auto mode works to a target of 5.6 or **6.7 mmol/L**. For exercise, can set a temp target of 8.3mmol/L (can do this 2 hours beforehand)

- **<u>Safe basal mode is entered if:</u>**
  - Auto mode at min delivery for at least 3hrs
  - Auto mode at max delivery for 7 hours
  - Sensor reading not available <u>or</u> sensor calibration expired.
  - Sensor might be reading lower than your actual glucose values
  - With sensor change, pump will switch to safe basal
  After 4 hours in safe basal, with no SG readings or BG entry, pump will exit to manual mode

- **<u>Returning to Auto-mode:</u>**
  When you have automatically transitioned to manual mode, you can return to auto-mode automatically **IF:**
  - Sensor is providing good SG values
  - Auto-mode is not in warm-up period.
  N.B. if any of these conditions not met, you need to provide a meter BG, <u>or</u> you may be locked out of Auto-mode until a five-hour warm-up period has passed.

Contact study staff for any study or pump related problems, on xxxx xxxx

AUTO-MODE ALARM - ALERTS & MESSAGES:

- ***Calibration required***: a BG meter reading is needed immediately to calibrate your sensor so you can continue receiving sensor readings. Check meter BG & calibrate sensor.

- ***High BG XX mmol/L:*** BG just entered is above 13.9mmol/L. Wash hands. Check infusion set. Check ketones. Confirm BG.

- ***High SG:*** SG has been high for over three hours. Check infusion set. Check ketones. Monitor BG.

- ***Low SG x.xx mmol/L:*** SG is under 2.8mmol/L. Perform meter BG and treat as needed. Monitor BG

- ***No sensor signal:*** no transmitter signal received for 30 mins. Move pump closer to transmitter – *can take up to 15 mins for pump to reconnect.*

- ***Auto Mode Max delivery***: Auto-mode has been at max delivery for 7 hours. Enter BG to stay in Auto Mode.

- ***Auto Mode Min delivery***: Auto-mode has been at min delivery for 3 hours. Enter BG to stay in Auto Mode.

- ***Sensor updating***: do not calibrate unless notified. This could take up to 3 hours.

- ***Active insulin up-date***: this can take up to five hours.
  Reasons for active insulin update are: complete pump reset (caused by loss of battery power), software error, or following a Suspend lasting four hours or longer.

HCL to Improve Glycaemic Control Interview Guide (PCH only)

Participant ID _____

Date _____ / _____ / _____

➢ Now that you have completed the study, we would like to hear about your experience using the study pump and being in auto-mode.
➢ Your participation is voluntary, you can choose not to answer questions or we can stop the interview at any time.
➢ The interview will be audio recorded so it can be transcribed later. No identifiable information will be included.
➢ This should take about 40 minutes; you can take a break at any time
➢ Are you happy to continue?

1. Tell me about your diabetes – What is diabetes like for you?

Prompts:
How long have you had diabetes?
What are some of the hardest things about diabetes?
Have you had times where diabetes has not been your priority? Tell me about that
Explore clinic attendance/other sources of support. Is there anything you find easy about your diabetes?

2. May I ask about your glucose control?
Prompts:
What was your glucose control like prior to starting in the study?
Hospital admissions
Previous use of technology (sensors / pumps)
What makes diabetes easier? Support from parents/ friends/ being left alone??
Did using the study pump and being in auto mode impact your diabetes management – How/why?
Any noticeable changes in your glucose control during the study?
Hypoglycaemia / hyperglycaemia

3. Why did you join this study?
Prompts:
What do you think of the study pump?   What features did you like? What features didn't you like?
Would you recommend the study pump and using auto mode to other people with T1D? Why
Did this study have any effect on your diabetes management? If so, how?

4. May I ask do you normally do exercise?
If no – what stops you from exercising?
If yes - Tell me about your exercise before coming into the study.
During the study period did your exercise change? If so, how?
Prompts:
Did exercise type, frequency or intensity change? Why do you think this is?
Did you stay in auto mode while exercising? Do you take your pump off for exercise?
Did you experience post-exercise hypoglycaemia?

5. Tell me about your sleep?

Prompts:

How would you describe your sleep prior to starting the study? And during the study?

Did the study pump help / hinder?

Explore how and why …

6. Tell me about eating and using the study pump in auto mode?

Prompts:

How would you describe your eating prior to starting the study? And during the study

Did auto mode help / hinder?

Did bolusing improve or did the system let you 'get away' with missed boluses?

Explore what and why …

7. Thinking about the HCL system

How happy / comfortable were you using automode?

How was this different to your normal pump management? Explore problems

You have been on pump therapy 24/7 but for you to be in automode, you need to wear a sensor. Do you think one can wear a sensor all the time?

- If no – why? What might make it easier to wear a sensor more often?

8. Thinking about the support you received from the study Diabetes Educator during the 6 month study period

How did you find the contact you had from the study Diabetes Educator?

Do you think your management was better or worse while you were in touch with DE?

Explain why /how

Ask about Frequency of contact with DNE

Ask about timing of contact – need more/less

Any suggestions around this

9. Can you think of anything about the study pump you would change if you could?

Device alarms / notifications

Corrections

10. Last question, may I ask, does diabetes ever get you down?

Prompt:

General management

Diabetes distress/ burnout

Support persons

Explore emotion as they come up….

If participants appear distressed or verbalise that they are distressed remind participants they can see their GP who can complete a mental health care plan which will allow access to psychological services via Medicare and facilitate a referral. Alternatively they can speak with their endocrinologist for referral to psychological services as needed.

Phone Interview Guide (All Sites – Opt in/out)

I. Overall Feelings about the AHCL System (20 minutes)

Let's talk about your overall experience with the hybrid closed loop system you have been using during this clinical trial.

1. I'd like to understand how you feel about using the system during the trial. First, I'd like to start with your satisfaction. That is, if you like or dislike certain things about it. Can you give me some examples?
   a. Are there positive things about Auto Mode, if so what is it?
   b. So you said some positives, are there anything negatives?

2. How well do you think you know how the product is working? Are there any problems that you are running into?
   a. [IF YES] what do you do when you run into these problems?
   b. [Skip this if they are on 3.0] Are you aware of a feature called auto correction? Do you know what it is?
      a. Can you share with me your experience with it? [trust, during sleep, etc.]
      b. [If yes] Do you know when and why you are receiving auto corrections? How do you know?

3. What is your level of trust with the system, in scale of 1-5 (5 being fulling trusting it)? Can you give me some examples why you rated that way?
   a. What would have helped you gain trust sooner or at all?
   b. How do you know if the system is doing its job right or you can trust it? [any visual indication]

4. During the study, has there been any moments that you were not sure what to do? [not sure to either intervene or let the system take control] What did you do in this situation?

5. Now let's talk about how you feel about high blood sugars on this product. Do you feel any difference? For example, after meals?
   a. Do you feel this system can handle your highs successfully?

6. Let's hear about your night time experience? Anything you are concerned about?

7. How do you think using Auto Mode has changed the way you manage your diabetes day to day? Is it harder/easier? More time vs. less time?
   a. Can you give me specific examples?

8. Now I want to hear about how you like the user interface. Can you tell me little bit about your experience using the user interface, menus, graphs, etc.? Anything you would change about it?

9. What was your biggest unanswered question when you first began using the device? Anything that you wish you knew before starting the system?

10. How was your experience eating meals while using the system?

II. Closing (2 minutes)

11. What advice would you give someone who is starting Advanced Hybrid Closed Loop in order to be successful?

12. Is there anything you would like to share about the Advanced Hybrid Closed Loop system that we haven't discussed?

Thank you for your time and your participation.