Adult Hybrid Closed Loop Study (HCL Adult) Statistical Analysis Plan

Study title: Evaluation of the efficacy and cost-effectiveness of long-term hybrid closed loop insulin delivery in improving glycaemia, psychological wellbeing, sleep quality, cognition, and biochemical markers of vascular risk in adults with type 1 diabetes compared with standard care

Short title: HCL Adult

Investigational device: Medtronic MiniMedTM 670G hybrid closed loop system

Funding: JDRF Australia T1DCRN

Study sites: St Vincent's Hospital Melbourne, Fitzroy VIC

Royal Melbourne Hospital, Parkville VIC

The Alfred, Melbourne VIC

Westmead Hospital, Westmead NSW

Repatriation General Hospital, Daw Park SA

Sir Charles Gairdner Hospital, Nedlans WA

Royal Hobart Hospital, Hobart TAS

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Section 1: Administrative information

Trial and trial registration

Trial title: Evaluation of the efficacy and cost-effectiveness of long-term hybrid closed loop insulin delivery in improving glycaemia, psychological wellbeing, sleep quality, cognition, and biochemical markers of vascular risk in adults with type 1 diabetes compared with standard care
Trial registration number: ACTRN12617000520336.

Ethics approval: St Vincent's Hospital Melbourne Human Research Ethics Committee (lead site, approval number HREC-D 088/16).

SAP version

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Prepared according to Guidelines for the Content of Statistical Analysis Plans in Clinical Trials [1].

Protocol version

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Protocol published: McAuley SA, de Bock MI, Sundararajan V, et al. Effect of 6 months of hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol. BMJ Open 2018;0:e020274. doi:10.1136/bmjopen-2017-020274 [2]

SAP revisions

None

Roles and responsibilities

Principal investigator: Prof David O'Neal (St Vincent's Hospital Melbourne, VIC)

Study statistician: Sara Vogrin (The University of Melbourne, VIC)

Study coordinator: Catriona Sims (The University of Melbourne, VIC)

Investigators (in alphabetical order):

Prof L. Bach (The Alfred, VIC)

Assoc Prof M. Burt (Repatriation General Hospital, SA)

Prof P. Clark (The University of Melbourne, VIC)

Assoc Prof N. Cohen (Baker IDI Heart and Diabetes Institute, VIC)

Prof P. Colman (Royal Melbourne Hospital, VIC)

Dr R. McCallum (Royal Hobart Hospital, TAS)

Dr C. Hendrieckx (The Australian Centre for Behavioural Research in Diabetes, VIC)

Assoc Prof D. J. Holmes-Walker (Westmead Hospital, NSW)

Prof A. J. Jenkins (University of Sydney, NSW)

Prof T. Jones (Princess Margaret Hospital for Children, WA)

Dr J. Kaye (Sir Charles Gairdner Hospital, WA)

Prof A. Keech (University of Sydney, NSW)

Dr K. Kumareswaran (The Alfred, VIC)

Dr M. H. Lee (St Vincent's Hospital Melbourne, VIC)

Prof R. J. MacIsaac (St Vincent's Hospital Melbourne, VIC)

Dr S. A. McAuley (St Vincent's Hospital Melbourne, VIC)

Dr B. Paldus (St Vincent's Hospital Melbourne, VIC)

Prof J. Speight (The Australian Centre for Behavioural Research in Diabetes, VIC)

Assoc Prof S. Stranks (Repatriation General Hospital, SA)

Prof V. Sundararajan (La Trobe University, VIC)

Dr S. Trawley (The Australian Centre for Behavioural Research in Diabetes, VIC)

Prof G. M. Ward (St Vincent's Hospital Melbourne, VIC)

Signatures

Principal investigator: Prof David O'Neal

Signature:  Date: 25/10/2019

Study statistician: Sara Vogrin

Signature:  Date: 23/10/2019

Section 2: Introduction

Background and rationale

Type 1 diabetes is a chronic condition affecting over 120,000 Australian people with the incidence increasing each year [3]. The goal of treatment is to maintain glucose levels in a healthy range, as departures in either direction are associated with numerous acute and chronic complications. Even with advances in treatment, the condition and the management itself still have a significant impact on quality of life [4].

The core strategy in type 1 diabetes management is insulin replacement, which is generally delivered subcutaneously via either multiple daily injections (MDI) of insulin administered by the person with diabetes or insulin pump therapy (IPT) which delivers a pre-specified basal dose of insulin continuously and allows a person with diabetes to administer extra doses when required (such as before meals and to correct elevated glucose levels) [5].

A recent improvement in treatment is the development of hybrid closed loop (HCL) systems which integrates an insulin pump, and continuous glucose monitoring (CGM) system with an insulin dosing algorithm. Basal insulin delivery is thus automatically adjusted to concurrent glucose levels. However, adjustment of insulin dosing for meals, to correct high glucose levels and to account for exercise still require intervention by the person; therefore, these systems are termed 'hybrid' [6].

There have been numerous studies examining short-term (up to 3 months) effectiveness of HCL systems, with a meta-analysis reporting an absolute increase in % time in target glucose range of mean (95% CI) 11.1 % (6.9, 15.2) compared with conventional IPT [7].

The purpose of the Adult Hybrid Closed Loop Study (HCL-Adult) is to evaluate the effectiveness of long-term hybrid closed loop insulin delivery (6 months) in adults with type 1 diabetes compared to standard care (either MDI or IPT). The goal of this study is to evaluate the effect of this new treatment modality on glycaemia, psychosocial well-being, sleep quality, cognitive functioning and biochemical markers of vascular risk as well as its cost-effectiveness.

Objectives

Primary

To determine the effectiveness of 6 months closed-loop compared with manually determined insulin dosing (without real-time CGM) on time-in-target glucose range in adults with type 1 diabetes.

Secondary

To determine the effectiveness of 6 months closed-loop compared with manually determined insulin dosing on glucose control, psychosocial well-being, sleep, cognitive functioning, ECG and health economics measures in adults with type 1 diabetes.

Section 3: Study Methods

Trial design

HCL-Adult is a multicentre, open label, parallel-group, superiority randomized clinical trial with equally sized treatment groups.

The intervention will last for 26 weeks, with an additional minimum 5 week period of active run-in which includes education (pre-randomisation). The exact duration of run-in will depend on individual training requirements. The study flow is presented in Figure 1.

Randomization

Group allocation (HCL or continuing standard care) will be random with a 1:1 ratio using minimization with 3 stratification variables, all of which are expected to be highly prognostic of primary outcome. These minimization variables are: 1) % time in target range pre-randomisation (dichotomised into <= 55% and > 55%); 2) study centre (7 sites); and 3) insulin delivery modality at enrolment (MDI or IPT). Due to the nature of the intervention, blinding of participants and investigators is not possible.

Sample size

Sample size calculation is based on a parallel design with 2 equally sized groups.

Assumptions used were derived from JDRF CGM randomized clinical trials [8, 9] that recruited a sample of 69 adults (25-70 years old) with type 1 diabetes and a baseline HbA1C < 10.5%, 86% of whom were using IPT and 14% using MDI. All participants had masked CGM data at randomization and at 6 months. Study investigator Professor Roy Beck, personal communication, provided estimates of the effective standard deviation of percentage time spent in target glycaemic range at 6 months (adjusted for baseline) which was 9% (95% CI 8% to 12%) for pump users and 10% (95% CI 7% to 19%) for MDI users.

To detect a difference in percentage time in target glycaemic range of 5% with 80% power and 5% type I error rate assuming a common standard deviation of 9%, a total of 104 participants are needed. Allowing a drop-out rate of 10% a total of 120 people will be recruited, 60 randomized to HCL while 60 randomized to control group.

A more conservative scenario with a dropout rate of 20%, and unequal SDs of 12% and 19% for IPT and MDI users, respectively, increases the minimum detectable absolute difference to 9% with a power of 80%.

Framework

This study is a superiority study with all analysis being performed on this basis.

Statistical interim analyses and stopping guidance

No interim analysis is planned. The study device has been previously proven to be safe for people with type 1 diabetes [10]; therefore, early stopping due to safety issues is not expected. However, safety recommendations will be made by an independent Data Safety Monitoring Committee (DSMC).

Timing of final analysis

The primary outcome and secondary glucose outcomes will be analysed collectively at the conclusion of the study. Other secondary outcomes will be analysed separately at the end of the study.

Health economic outcome and biomarkers will be analysed at a later date after additional funding is obtained.

Timing of outcome assessments

Pre-randomisation outcomes are collected at Visits 3-6, mid-study outcomes are collected at Visits 9-11 and end-of-study outcomes are collected at Visits 12-15 (Figure 1)

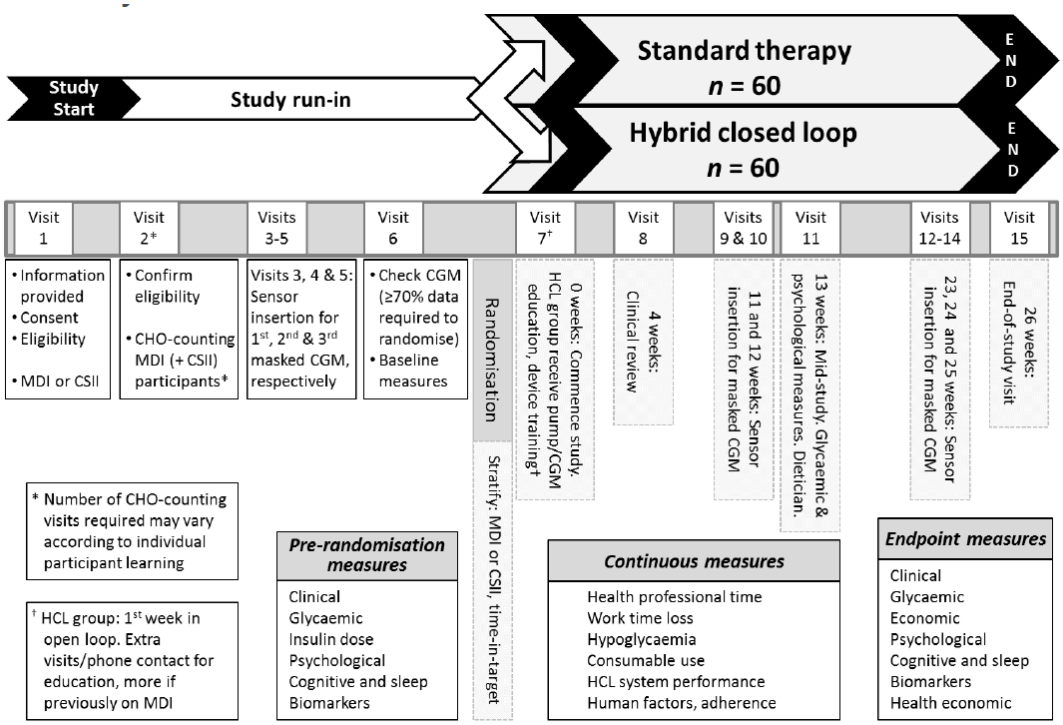

Figure 1: Study flow and timing of outcome assessments

Section 4: Statistical principles

Confidence intervals and *p* values

All hypothesis testing will be two-sided with an α of 0.05, with reported 95% confidence intervals.

No corrections for multiplicity are planned to control Type I error; rather, the effectiveness of the intervention will be assessed based on the clearly specified primary outcome; secondary outcomes are exploratory in nature and will be labelled as such in publications arising from the study. A transparent approach to reporting results will be taken, with the list of all pre-specified secondary outcomes included in every publication resulting from this study (this list would include a reference to relevant publication if results already published).

Results will be interpreted in light of the number of comparisons and where multiple comparisons indicate multiple effects, the consistency of these results will be discussed.

Adherence and protocol deviation

The primary analysis for this study will take an intention-to-treat approach; data from all participants will be analysed. Overall adherence to intervention in this setting is difficult to assess as it is composed of participant's adherence as well as system performance. CGM use will be used as a surrogate marker of participant's adherence to intervention – reported as the proportion of overall time that CGM was active with available glucose readings. This will be interpreted with caution as it will include technical issues beyond participant's control. HCL performance parameters (such as % time closed loop is active) are part of secondary analysis. These results will also be interpreted with caution as they are intertwined with participant's adherence.

No adherence parameters will be reported for the control population.

Protocol deviation was defined as a breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree the safety or rights of a research participant or the reliability and robustness of the data generated in the research project.
The number and details of protocol deviations and violations will be presented as were reported by the study site.

Analysis populations

Entire study population

The entire study population is defined as all participants who were randomized (and have thus completed the run-in period of the first 6 visits of the study) regardless of their eligibility, deviations from protocol or adherence to intervention. Participants will be analysed according to the treatment arm to which they were randomised.

Complete case population(s)

The complete-case population is defined as all participants who were randomized to a treatment group for whom outcome data were available for analysis.

Note: given different patterns in missing data over different outcomes, the membership of each complete-case population differs based on the outcome being analysed.

Per protocol population

Per protocol population will exclude participants who:

- had the intervention (HCL) active for < 80% of the intervention period (auto-mode for less than 80% of time from randomisation to the end of the study due to either non-adherence to protocol or technical issues)
- standard treatment wearing real-time CGM (with or without alarms) at any time during the study
- wearing less than 3 or more than 5 masked CGM sensors at baseline and end of study

Safety population

All participants enrolled in the study, whether randomised or not, including those who withdrew prior to the randomisation.

Section 5: Trial Population

Screening data

Screening data has not been collected.

Eligibility

Trial inclusion and exclusion criteria are reported in the protocol [2]. Number of ineligible patients who were enrolled and randomised will be reported together with their reasons for ineligibility.

Recruitment

Recruitment will aim to obtain an equal proportion of people using MDI and IPT. CONSORT diagram will be presented (Figure 2).

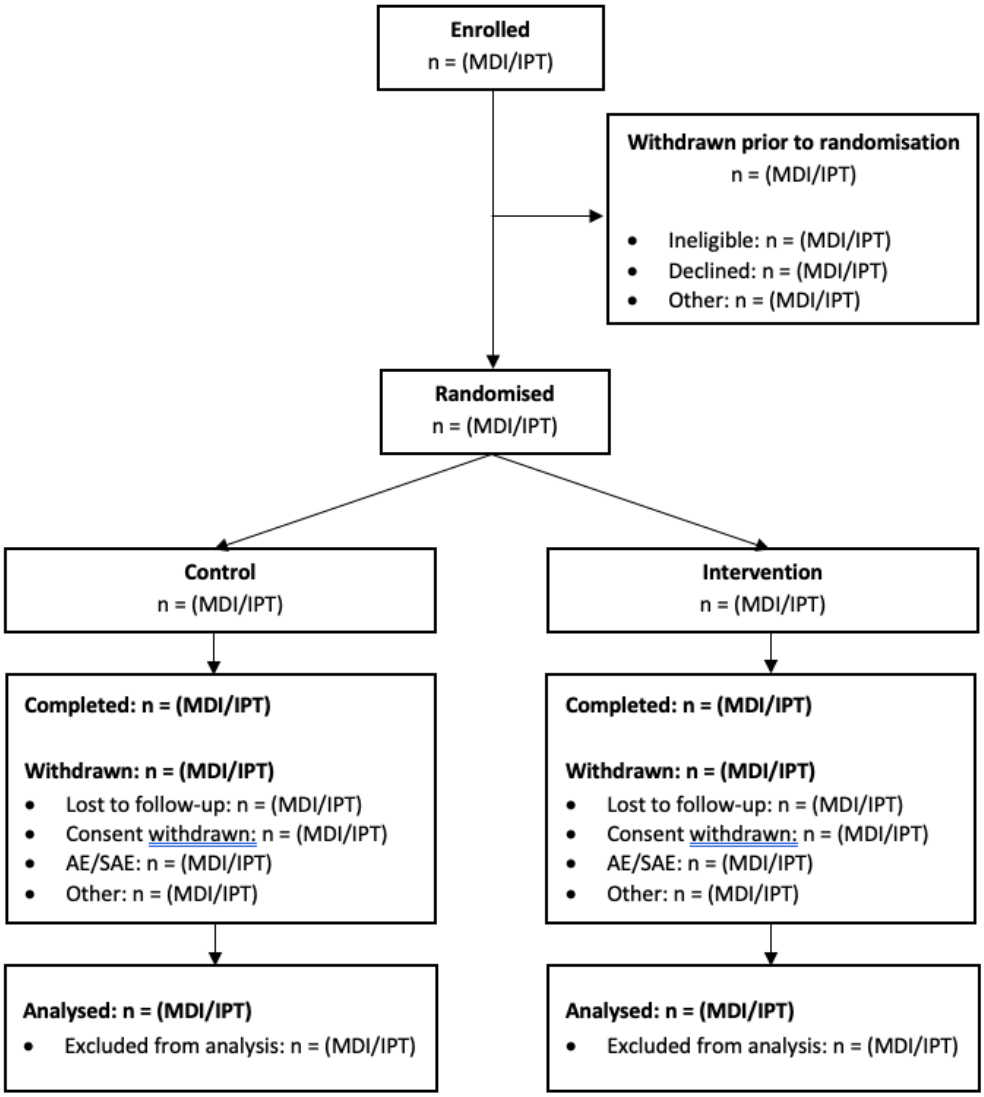

Figure 2: Example of CONSORT diagram

Withdrawal/follow-up

Withdrawals will be reported as indicated in the CONSORT diagram above.

Timing of withdrawals for each category will be presented in a separate table (each cell will contain number of withdrawn participants):

Visit	Overall	IPT		MDI	
		Intervention arm	Standard arm	Intervention arm	Standard arm
V1					
V2					
V3					
V4					
V5					
V6					
V7					
V8					
V9					
V10					
V11					
V12					
V13					
V14					
V15					
V16					

Baseline participant characteristics

Participants' pre-randomisation characteristics will be presented in a table, separately for each arm of the study (control arm, intervention arm). Categorical characteristics will be presented as frequency (%) and continuous as median (IQR) [min, max] or mean (standard deviation) [min, max], depending on the distribution.

The following variables will be included:

- Age
- Sex (Male vs Female)
- Insulin delivery modality (MDI vs CSII)
- Study site
- Time in target range at randomisation (<= 55%, > 55%; and as continuous variable)
- Duration of diabetes (years)
- Pump duration (years) – for CSII group only
- Weight (kg) at randomisation
- BMI (kg/m2) at randomisation
- HbA1c at enrolment (%, mmol/mol)
- HbA1c at randomisation (%, mmol/mol)
- C-peptide (fasting) at enrolment

- Total daily insulin (units) at enrolment
- Basal insulin proportion (%) at enrolment
- CHO-counting (yes vs no) at enrolment
- Gold score indicating hypoglycaemia awareness at randomisation
- Microvascular complications at enrolment
- Macrovascular complications at enrolment
- History of diabetic foot ulcer at enrolment
- Diabetic ketoacidosis in the year prior to enrolment
- Severe hypoglycaemic episodes in the year prior to enrolment

Formal statistical comparison of baseline characteristics between groups will not be performed, rather clinical importance of any imbalance will be noted.

Section 6 Analysis

Primary outcome

Outcome definition

Primary outcome is the percentage of time spent in target glucose range (3.9-10 mmol/L) measured by masked CGM over 3 weeks starting at 23 weeks post randomization (± 3 weeks) (glucose measured at 5-min intervals). Participants with a low number of available CGM readings in one or more weeks will have the CGM repeated and may have up to 5 weeks of masked CGM collection. To accurately represent participant's glycaemic status, only days with at least 70% valid CGM readings will be used (>= 202 valid readings) [11]. The percentage of time spent in target glucose range will be calculated by dividing the number of sensor readings falling in the range 3.9 – 10 mmol/L by the total number of sensor readings and multiplying by 100 over the whole period of masked CGM collection. If the participant has less than 10 representative days [11] their outcome will be counted as missing (individual glucose values will not be imputed).

Analysis methods

To test for an effect of the treatment group on the primary outcome, an ANCOVA including treatment arm and baseline percent time in target range will be conducted. The primary outcome will be analysed on an intention-to-treat basis on the entire study population with missing outcome data imputed using multiple imputations under missing at random (MAR) assumption (overall time in range will be imputed rather than single glucose values, see section on Missing data).

Results will be presented as the mean difference in the percent time in target range between treatment arms at the end of the study with 95% confidence interval and p value.

Model residuals will be visually inspected to test the assumptions of the model. In the event of violations to homoscedasticity and non-normal distribution, the outcome will be transformed using a natural logarithm. If the ANCOVA model still displays poor fit, non-parametric analysis (Wilcoxon rank sum test) will be employed.

Sensitivity analyses

1. ANCOVA with adjustment for factors used in the minimisation will be conducted (study centre – 7 categories, insulin delivery modality – 2 categories).
2. Replication of primary outcome analysis in complete case population (missing completely at random (MCAR) assumption)
3. Replication of primary outcome analysis in full study sample using multiple imputation of missing data under missing not at random (MNAR) assumption (see section Missing data)
4. Replication of primary outcome analysis in per-protocol population (see population definitions).

Planned subgroup/interaction analyses

The differential effect of the intervention on the primary outcome based on insulin regimen at enrolment (IPT or MDI) will be examined using a linear regression including terms for treatment group, regimen, a treatment group by regimen interaction, and baseline time in range.

Missing data

See Missing data section below.

Secondary outcomes

1. Glucose control

Outcome definition

- Percent time in ranges (day/night/overall)

Percent time spent in the following ranges will be examined.

- 3.9 – 10.0 mmol/L
- < 2.8 mmol/L
- < 3.0 mmol/L*
- < 3.3 mmol/L
- < 3.9 mmol/L
- 3.9 – 7.8 mmol/L
- > 10.0 mmol/L
- > 13.9 mmol/L
- > 16.7 mmol/L

*This outcome was not part of initial protocol, however it was added due to the position statement of the American Diabetes Association and the European Association for the Study of Diabetes published in 2017 ([12])

Percentage of time spent in each glucose range will be calculated by dividing the number of sensor readings falling in the range by the total number of valid sensor readings and multiplying by 100. This will be performed separately for day (6:00 –23:59), night (00:00 – 5:59) and overall. Values will be calculated at baseline, mid-study, and end-of-study using masked CGM collection.

- Mean glucose level, standard deviation and coefficient of variation (SD/mean)

These metrics will be calculated using valid readings only, separately for day (6:00 – 23:59), night (00:00 – 5:59) and overall. Values will be calculated at baseline, mid-study, and end-of-study using masked CGM collection.

- Fasting capillary blood glucose

Fasting capillary blood glucose is defined as the first capillary blood glucose taken between 5 am and 9 am during the period of masked CGM collection. These are recorded separately in blood glucose meters.

- HbA1c

HbA1c is measured from blood sample at enrolment, randomisation, mid-study (3 months post randomisation) and end-of-study (6 months post randomisation).

- 1.5-anhydrogluticol

This biomarker is measured at randomisation and end-of-study.

- Hypoglycaemic events

Events of symptomatic hypoglycaemia are defined as episodes of hypoglycaemia with glucose level < 3.5 mmol/L confirmed by a finger prick and requiring carbohydrate rescue. These events are self-reported and collected in participant's diary throughout the study.

Analysis method

All secondary outcomes (except fasting capillary blood glucose and number of hypoglycaemic events) will be analysed using ANCOVA including treatment and baseline score of the outcome. Where the distribution of residuals is heteroscedastic even after logarithmic transformation, a Wilcoxon rank sum test will be performed (in which case no adjustments for baseline will be performed). With parametric methods, mean differences with 95% CI will be presented, whereas with non-parametric methods, median difference with 95% CI will be presented ([13]).

A mixed effects linear regression will be used to analyse fasting capillary blood glucose with random intercepts for individuals and study arm as a fixed effect.

The number of hypoglycaemic events will be analysed using Poisson regression or negative binomial regression if overdispersion is apparent.

Percent time in ranges, mean glucose, standard deviation and coefficient of variation will be performed separately for day (6:00 – 23:59) and night (0:00– 5:59).

All analyses will be performed separately for mid-study and end-of-study data.

Sensitivity analysis

Due to exploratory nature of the outcomes, no sensitivity analysis will be performed.

Subgroup analysis

To estimate the effect of the intervention based on regimen (IPT or MDI), a treatment group by regimen interaction will be included in all models. Where non-parametric analysis will be performed, each regimen will be analysed separately.

2. Clinical outcomes

Outcome definition

- Change in average total daily dose of insulin and basal/bolus proportions taken over the last 7 days
- Change in insulin-to-carbohydrate ratio (ICR) (ICR is usually expressed in 1:X form where X represents grams of carbohydrates covered by 1 unit of insulin. This ratio can be constant throughout the day or can vary for breakfast, lunch and dinner times. It will be analysed separately for breakfast, lunch and dinner time, as well as a weighted average overall for the day)
- Change in body weight (kg)

All clinical outcomes are measured at randomisation, mid-study and end-of-study.

Analysis method

Linear regression will be used to evaluate the effect of treatment arm on the change score from baseline. Where the distribution of residuals is heteroscedastic even after logarithmic transformation, rank sum test will be performed.

All analysis will be performed separately for mid-study and end-of study.

Sensitivity analysis

Due to exploratory nature of the outcomes, no sensitivity analysis will be performed.

Subgroup analysis

To estimate the effect of the intervention based on regimen (IPT or MDI), a treatment group by regimen interaction will be included in all models. Where non-parametric analysis will be performed, each regimen will be analysed separately.

3. Psychosocial, sleep and cognitive functioning

Outcome definition

- Psychological wellbeing
    - Hypoglycaemia Fear Survey II short form (HFSII-SF)
        - Behaviour subscale (0 to 20)
        - Worry subscale (0 to 24)
    - Hypoglycaemia Avoidance Scale (HAS) (currently being validated, therefore scales might change)
        - Behaviour subscale (0 to 48)
        - Worry subscale (0 to 48)
    - Problem areas in diabetes (PAID)
        - Total (0 to 100)
    - Diabetes positive wellbeing (W-BQ28)
        - Total (0 to 12)
- Quality of life
    - DAWN impact of diabetes profile (DIDP)
        - Total (1 to 7 for each dimension; and for total score)
- Treatment satisfaction
    - Diabetes treatment satisfaction questionnaire (DTSQs)
        Total (0 to 36)
    - Diabetes treatment satisfaction questionnaire (DTSQc)
        Total (– 18 to +18.)
- Sleep quality
    - Pittsburgh sleep quality index (PSQI)
        - Total (0 to 21)
    - Psychomotor Vigilance Test (averaged over visits 3-4, 9-10 and 12-13)
        - Average reaction time
        - Total number of lapses (response times above 500 milliseconds)
        - Average of the fastest 10% and slowest 10% of responses
    - Karolinska Sleepiness Scale (averaged over visits 3-5, 9-11 and 12-14)
        - Average Score 1 to 9
    - Actigraphy and sleep diary (averaged over visits 3-5, 9-11 and 12-14)

        - Average sleep time
        - Average sleep efficiency (time asleep / total time in bed)
        - Average sleep onset latency
- Memory
    - Prospective-retrospective memory questionnaire (PRMQ)
        - Total (16 to 80)

Analysis method

All outcomes will be analysed using ANCOVA including intervention group and baseline outcome score. Model residuals will be visually assessed to ensure assumptions are met and a logarithmic transformation of the outcomes will be performed in the presence of heteroscedasticity or non-normally distributed outcomes. A non-parametric analysis will be used if model assumptions are violated. The mean difference in outcomes with 95% confidence intervals will be presented for parametric analyses and the median difference in outcomes with 95% confidence intervals for non-parametric analyses.

Sensitivity analysis

No sensitivity analysis will be performed.

Subgroup analysis

The difference in intervention effects by regimen (IPT or MDI) will be explored by including regimen and the interaction between treatment group and regimen into the models. Each regimen will be analysed separately if non-parametric analysis is used.

4. Electrocardiographic profile

Statistical analysis plan for the analysis of electrocardiographic profile will be published separately in the future.

5. Human-technology interaction

Outcome definition

Participant perceptions of the HCL system assessed via short message service (SMS) data collection.

Participant expectations and experiences with the HCL system assessed via longitudinal semi-structured interviews (three Melbourne sites only).

Analysis method

Due to the exploratory nature of the data, descriptive statistics will be reported.

Thematic analysis of semi-structured interviews will be conducted.

Sensitivity and subgroup analysis

Not applicable

6. Health economic

Statistical analysis plan for health economic outcomes will be published separately in the future.

7. Biochemical markers of vascular disease risk

Statistical analysis plan for biochemical markers will be published separately in the future.

8. Hybrid closed-loop system performance parameters

Outcome definition

The following will be collected over the entire six-month study period for the intervention arm only:

- Proportion of time closed loop active
- Unplanned exits from closed loop (n)
- Unplanned replacement of insulin pump (n)
- Sensor failures (n)
- Reported insulin delivery line failures (n)
- Participant calls to the technical help line (n)
- Mean absolute relative difference (MARD) between sensor vs blood glucose meter readings
    - MARD will be calculated as a mean of relative difference $\left(\frac{|SGL-BGL|}{BGL} * 100\right)$ between fingerprick glucose reading and preceding sensor glucose reading (provided the sensor glucose was within 5 minutes of fingerprick glucose)

Analysis method

Descriptive statistics will be reported (frequency of events and number (proportion) of participants experiencing at least one event, MARD and % time closed-loop active will be presented with median and interquartile range).

Sensitivity analysis

Due to exploratory nature of the outcomes, no sensitivity analysis will be performed.

Subgroup analysis

No subgroup analysis will be performed.

9. Safety

Outcome definition

- Hospitalisations for diabetic ketoacidosis (n)
- Severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions (n)
- Infections and inflammation at sensor and insulin delivery line insertion sites

Analysis method

Safety outcomes will be presented as a count of events for each treatment group and percentage of participants experiencing at least one event in each treatment group. No formal statistical tests will be performed.

Sensitivity analysis

Due to exploratory nature of the outcomes, no sensitivity analysis will be performed.

Subgroup analysis

Separate analysis for each regimen will be performed.

Missing data

Baseline variables are expected to have minimal missing data. Missing data in outcome variables are more likely to be arbitrary missing than monotone missing, therefore missing data will be multiply imputed using a multivariate normal regression imputation method given smaller sample size [14]. All the imputations will be performed separately for each treatment arm [15]. Baseline and mid-study variables will be considered to be included in the model based on their correlation with the outcome. The number of imputations will be contingent upon the missing proportion: if $\leq$ 30% missing, 20 imputations will be generated; if >30% missing, 40 imputations will be generated [16].

In the event of violations to regression assumptions, hence non-parametric methods are required, simple imputation will be performed, replacing the missing value with the median of the treatment arm.

Secondly delta-adjusted multiple imputations will be conducted under the missing not at random (MNAR) assumption using the following deltas: -1SD, +1SD.

If unexpected patterns of missing data are found, additional post-hoc sensitivity analysis will be performed.

Additional analyses

1. Missing data patterns
   The patterns of missing data overall and within masked CGM will be explored, in particular time of the day and day of the week. Further analysis might be performed based on initial results.

2. Study process measures
   a. Time from enrolment to randomisation (days)
   b. Days between randomisation and end-of-study visit
   c. Amount and percent time valid sensor readings during masked CGM periods

   Median, interquartile range, minimum and maximum values will be presented overall and separately for each treatment group.

3. Meta- analysis on a combined dataset of adult and paediatric hybrid closed loop studies. The protocols of both studies have been aligned and have been published [2, 17]. Details of these analysis will be published separately.

Harms

Serious adverse events are analysed and reported regularly throughout the study to an independent Data Safety Monitoring Committee. The number of SAE (including details of each SAE) and the

number of participants experiencing at least one SAE are presented overall and separately for each type of SAE.

Statistical software

Analysis will be performed using Stata 15.1., R and R Studio.

Section 7 References

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