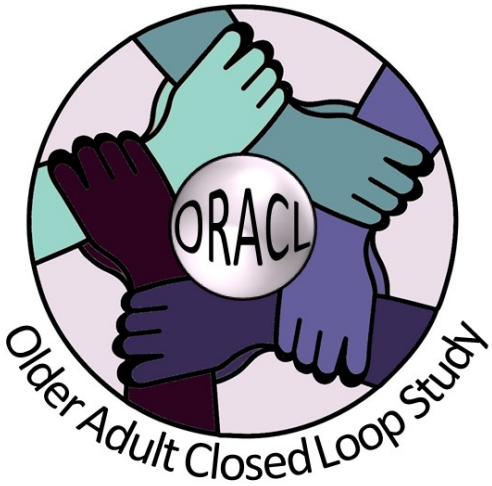

ORACL Study
Statistical Analysis Plan

Version 1.0

10 December 2020

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Study identifiers:
JDRF Grant Key: 3-SRA-2018-667-M-R
Trial registration number: ACTRN12619000515190

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LIST OF ABBREVIATIONS

CGM	Continuous glucose monitoring
CL	Closed loop
DKA	Diabetic ketoacidosis
HbA_{1c}	Glycosylated haemoglobin
MARD	Mean absolute relative difference
OL	Open loop
SAE	Serious adverse event
TIR	Time-in-range
IQR	Interquartile range

1. ADMINISTRATIVE INFORMATION

1.1 STUDY IDENTIFIERS

- Protocol: 1.3, 2 May 2019
- World Health Organization Universal Trial Number: U1111-1229-7168.
- Anzctr.org.au register Identifier: ACTRN12619000515190.
- JDRF Grant Key: 3-SRA-2018-667-M-R

1.2 REVISION HISTORY

Version	Date	Changes made to document	Authors
1.0	10 December 2020	Original version	Sara Vogrin, Sybil McAuley, Steven Trawley, Vijaya Sundararajan

1.3 CONTRIBUTORS TO THE STATISTICAL ANALYSIS PLAN

1.3.1 ROLES AND RESPONSIBILITIES

Names and OCRID	Affiliation	Role on study	SAP contribution
Sara Vogrin	Department of Medicine, The University of Melbourne	Trial statistician	Author
Dr Sybil McAuley	Department of Medicine, The University of Melbourne Department of Endocrinology, St Vincent's Hospital Melbourne	Principal Investigator	SAP review
Dr Steven Trawley	Cairnmillar Institute	Co-Investigator	SAP review
Professor Vijaya Sundararajan	Department of Public Health, La Trobe University Department of Medicine, The University of Melbourne	Co-Investigator	SAP review

1.3.2 APPROVALS

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention(s) being assessed).

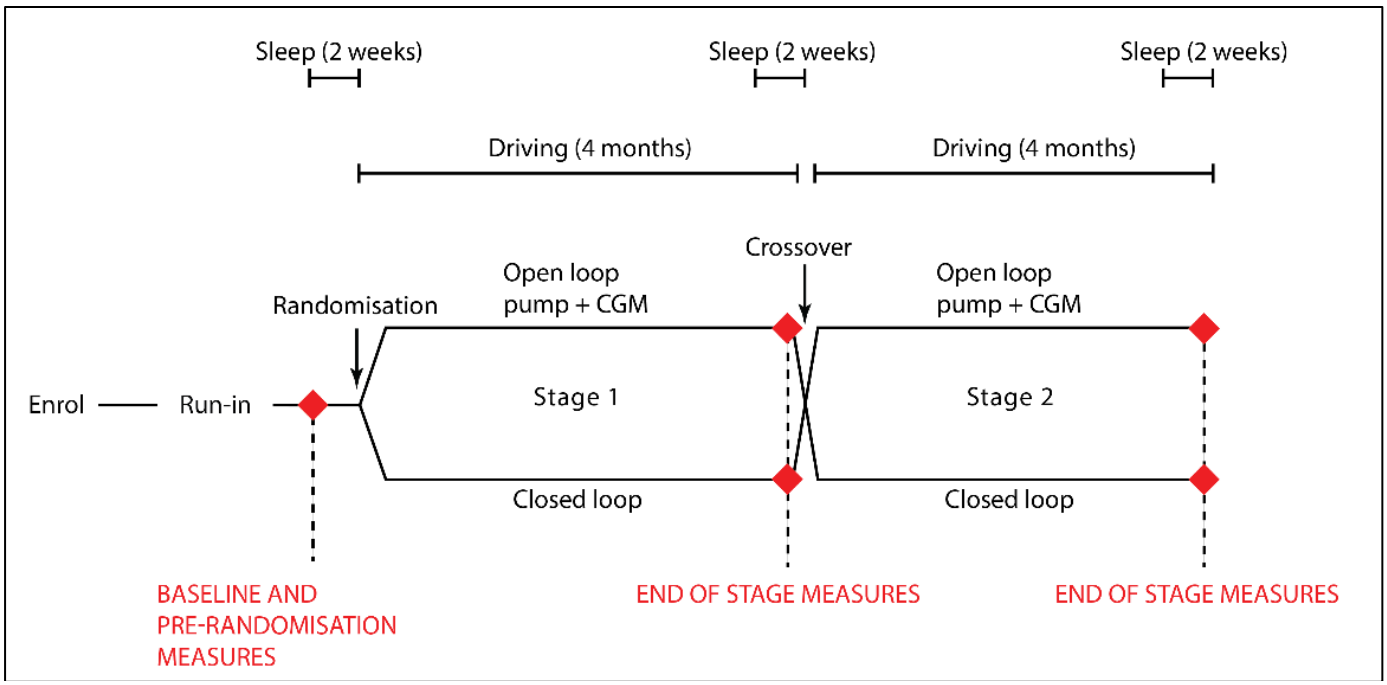
Sara Vogrin  10/12/2020

Dr Sybil McAuley  10/12/2020

2. STUDY SYNOPSIS

The ORACL Study is an open-label, two-stage randomised crossover study (AB/BA design) investigating the effect of closed loop (CL) vs open loop (OL) (pump + sensor) in older adults with type 1 diabetes. Each stage is of 4 months duration.

Outcomes include glucose and non-glucose parameters including physical well-being, cognitive functioning, psychosocial well-being, sleep, glucose patterns while driving, electrocardiograph profile and caregiver burden.



2.1 STUDY OBJECTIVES

2.1.1 PRIMARY OBJECTIVE

Proportion of time spent in sensor glucose target range (3.9–10.0 mmol/L) during CL versus OL stages, measured during the final 3 months of each stage (91 full days – midnight to midnight - backwards from the date of last stage visit).

We hypothesise that CL compared with OL therapy for older adults with type 1 diabetes will increase the proportion of time sensor glucose is in target range.

2.1.2 SECONDARY OBJECTIVES

Further glucose and non-glucose outcomes among older adults with type 1 diabetes. We will examine if CL vs OL:

- Reduces time above / below target glucose range, HbA_{1c} and glucose variability
- Reduces severe hypoglycaemia and diabetic ketoacidosis (DKA)
- Reduces diabetes-related hospitalisations and ambulance attendances
- Reduces incident falls, delirium, pressure sores and infections
- Reduces frailty and functional decline
- Improves cognitive function as reflected in task performance
- Increases psychosocial well-being and satisfaction with treatment
- Reduces fear of hypoglycaemia and diabetes distress
- Reduces caregiver burden
- Improves time in target glucose range while driving (to reduce risk of driving mishaps)
- Improves sleep quality and cardiac rhythm profiles.

2.2 PATIENT POPULATION

2.2.1 INCLUSION CRITERIA

- Age ≥60 years
- Type 1 diabetes for at least 10 years
- Insulin pump therapy (≥1 year pump experience) , with established insulin delivery settings
- HbA_{1c} ≤10.5% (≤91 mmol/mol)
- Able to use study devices and meet protocol requirements (+/- caregiver assistance)
- Treated with a rapid-acting insulin analogue
- English language proficiency
- Internet and cellular phone coverage at home
- Understands study protocol; willing and able to meet all protocol requirements

2.2.2 EXCLUSION CRITERIA

- Chronic kidney disease with eGFR <30 mL/min/1.73m^2 or on dialysis
- Use of glucose-lowering agent other than insulin within the past 3 months
- Corticosteroid medication within the past 3 months, or anticipated during the study period
- Clinically-significant gastroparesis
- Uncontrolled hypertension or thyroid disease, untreated malabsorption
- History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack, stroke, or thromboembolic disease in the past 3 months
- Clinical diagnosis of moderate or severe dementia
- Non-type 1 diabetes (including diabetes secondary to chronic disease)
- Use of CL insulin delivery within the past 3 months
- Inability to tolerate adhesives in the area of sensor placement (e.g. due to skin disease, intolerance to adhesives)
- Haemoglobinopathy, sickle cell disease, or has received red blood cell transfusion or erythropoietin within past 3 months
- Visual or hearing impairment precluding use of the study devices
- Any severe or unstable physical or psychological condition which, as judged by the Investigator, could compromise the ability to meet protocol requirements or interpretation of study results

2.3 OUTCOMES

2.3.1 PRIMARY OUTCOME

- Proportion of time spent in sensor glucose target range (3.9–10.0 mmol/L) during the CL versus OL stages, measured during the final 3 months of each study stage (91 full days – midnight to midnight - backwards from the date of last stage visit). This is calculated as the number of glucose readings within the target range divided by the total number of valid readings.

2.3.2 SECONDARY OUTCOMES

CL versus OL for the outcome measures listed below.

- Glucose
    - CGM metrics for 24 h/day, day [06:00–23:59] and night [00:00–05:59], measured during the final 3 months of each study stage:
        - Proportion of time 3.9–10.0 mmol/L (excluding the primary outcome)
        - Proportion of time <3.0 mmol/L
        - Proportion of time <3.3 mmol/L
        - Proportion of time <3.9 mmol/L
        - Proportion of time 3.9–7.8 mmol/L
        - Proportion of time >10.0 mmol/L
        - Proportion of time >13.9 mmol/L
        - Proportion of time >16.7 mmol/L
        - Mean glucose
        - Glucose variability: SD, coefficient of variation

- HbA_{1c}

- Clinical
  - Functional ability: Katz Activities of Daily Living [ADLs], Lawton-Brody Instrumental ADLs
  - Frailty: FRAIL, Mini Nutritional Assessment, Sarcopenia SARC-F, Walking Speed, Grip Strength, Physical Activity
  - Diabetes-related ambulance attendances
  - Diabetes-related hospitalisations
  - Incident falls
  - Incident delirium
  - Incident pressure sores
  - Incident infections
  - Severe hypoglycaemia
  - Diabetic ketoacidosis (DKA)
  - Total daily dose of insulin

- Cognitive functioning
  - Montreal Cognitive Assessment [MoCA]
  - Mini-Mental State Examination [MMSE]
  - Verbal IQ : National Adult Reading Test [NART]
  - Executive functioning: Trails Making Tasks B
  - Psychomotor speed: Symbol Digit Modalities Test, Trails Making Tasks A, Grooved Pegboard

- Psychosocial wellbeing
  - Pump technology – INSPIRE and INSPIRE partners (Visit 1: Baseline; end of CL: Post Assessment)
  - User friendliness of current pump
  - Fear of hypoglycaemia: Hypoglycaemia Fear Survey [HFS-II]
  - Hypoglycaemia awareness: Gold Score and Clarke score
  - Diabetes burden: Problem Areas in Diabetes short form [PAID-5], family member [PAID-5-DFM]
  - Depression: Geriatric Depression Scale: Short Form [GDS]
  - Impact of diabetes: DAWN Impact of Diabetes Profile [DIDP] and family members [DIDP-FM]
  - Participant and caregiver experiences assessed via semi-structured interviews

- Glucose patterns while driving (measured by CGM)

- Sleep
  - Pittsburgh Sleep Quality Index [PSQI]
  - Glucose patterns during sleep based on actigraphy and sleep diary data measured during the final two weeks of each stage.

- Electrocardiograph profile (measured via Holter monitor)
  - Corrected QT interval (QTc)
  - Cardiac arrhythmias

2.3.3 SAFETY OUTCOMES

Safety outcomes are included under the clinical secondary outcomes.

2.3.4 TERTIARY OUTCOMES

- CL system performance measures during the CL stage
  - Proportion of time CL is active
  - Number of CL exits
- Glucose sensor performance:
  - Accuracy: mean absolute relative difference (MARD), compared with reference capillary blood glucose
  - Reliability: display time (%)
  - Sensor failures

While reliability and sensor failures were planned tertiary outcomes, these will not be analysed due to insufficient data reported within the insulin pump.

2.4 INTERVENTION

The study's CL system will be a MiniMed™ 670G system (Medtronic, Northridge, CA, USA). The CL platform will comprise a glucose sensor (Guardian sensor3) and transmitter (Guardian Link3) for real-time CGM, an insulin pump (670G) with insulin delivery consumables, and an insulin delivery control algorithm.

The control stage uses this same 670G system in its "manual mode", without either automated delivery or predictive low-glucose suspend activated, throughout the OL study stage.

2.5 RANDOMISATION AND BLINDING

The order of study stages will be randomly assigned, stratified according to study site, using block randomisation with randomly permuted blocks. Randomisation procedures will be undertaken by the University of Melbourne. Randomisation will occur during Visit 4 (via the eCRF); therefore, allocation will be concealed from participants and site Investigators until that time.

2.6 SAMPLE SIZE

The power calculation is for a two-stage randomised crossover study design, with the primary outcome being improvement in time spent in glucose target range. With this study design, each participant will be their own control with the difference between CL compared to the individual's own OL measurements used as the primary response variable.

Assuming a SD of 13% which is consistent with our local CGM data for adults on pumps, a two-tailed test with a null hypothesis stating the difference between CL and OL of zero, and a type I error rate set to 5%, 24 participants are required to detect a minimum absolute difference of 8% time in glucose target range with 80% power. We plan to enrol up to 30 participants to allow for a 20% drop out rate. Participants who drop out of the study prior to randomisation will be replaced.

Mean %time CGM within the target range for study participants prior to randomisation was 70% with SD of 11.5 %. Using these estimates and assuming correlation between stages is 0.5, the minimal absolute detectable difference with 24 participants (20% drop off rate) is 7% and with 30 participants (no drop off) is 6%. If the correlation between stages is higher (0.7), then the minimal detectable difference will decrease to just under 5%.

3. STATISTICAL ANALYSIS

3.1 GENERAL PRINCIPLES

This statistical plan is applicable only to the primary outcome, and the following secondary outcomes: glucose outcomes, clinical outcomes, congnitive functioning, psychosocial wellbeing and sleep quality. The analysis plan for secondary outcomes of glucose patterns while driving and electrocardiograph profile will be prepared separately.

All analyses will be on intention-to-treat principle and will include all randomised participants. Additional analysis of the primary and secondary outcomes using two versions of per-protocol population (described under 'Data sets to be analysed') will also be performed.

While no subgroup analysis was specified in the study protocol, during the study it was decided that four subgroup analyses are of interest: impaired awareness of hypoglycaemia (classified as Clark score ≥4 and Gold score ≥4 separately) and undetectable C-peptide (classified as <0.01 and ≤0.03[1] separately).

All outcomes will be presented using descriptive statistics by stage as well as the mean (or median) difference between closed loop and open loop with 95% confidence intervals. All statistical tests will be 2-tailed with significance level set at 0.05.

All analysis will be performed using Stata 16.1.

3.2 INTERIM ANALYSES

No interim analysis will be performed. Recruitment and compliance to intervention will be regularly monitored throughout the study and reported to study investigators.

3.3 MULTIPLICITY ADJUSTMENT

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 publication.

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.

3.4 BLIND REVIEW

No blind review is planned.

3.5 DATA SETS TO BE ANALYSED

Analysis will use the intention to treat population, that is, all participants who were randomised.

The safety population will consist of all enrolled participants.

The per-protocol population will consist of all participants who were compliant with the intervention; that is, those who were in closed loop for at least 80% of time during the closed loop stage and at most 5% of time during open loop stage and participants whose each stage lasted at least 91 days.

Due to the COVID-19 pandemic and implemented movement restrictions, a large number of visits were conducted remotely, particularly at one site. Remote assessments were not regarded as a protocol violation; however, they may have an impact upon secondary, non-glucose outcomes, particularly outcomes that were unable to be measured remotely (e.g. grip strength, gait speed and grooved pegboard). Therefore, an additional per-protocol population will consists of participants who had final visit of both stages conducted in person.

3.6 SUBJECT DISPOSITION

A CONSORT flowchart will be presented which will include reasons for loss to follow-up and withdrawals.

3.7 PATIENT CHARACTERISTICS AND BASELINE COMPARISONS

Patient characteristics for all randomised participants will be presented using median (interquartile ranges) or mean (standard deviation) for continuous variables and frequency (percentages) for categorical variables. Additionally, characteristics of each sequence will be presented (CL-OL vs OL-CL). No statistical tests will be performed between randomization arms.

3.8 COMPLIANCE TO STUDY INTERVENTION

Compliance to study intervention will be measured by:

- length of the study stage (in days);
- CGM wear (% total time of the stage);
- number of days in each stage with at least 70% of valid readings; and
- % time closed loop active (% total time of the stage and % time CGM available).

Some of these variables are already tertiary outcomes.

3.9 CONCOMITANT THERAPIES

Given the nature of intervention, there are no concomitant therapies.

3.10 ANALYSIS OF THE PRIMARY OUTCOME

3.10.1 MAIN ANALYSIS

The primary outcome (difference between closed and open loop in %CGM time in target range) will be analysed by mixed effects linear regression model using restricted maximum likelihood estimation with unstructured covariance. Participants will be entered as random intercepts while intervention and period will be entered as fixed effects. The model fit will be estimated by visual inspection of the residuals and the outcome will be transformed using a natural logarithm, if required. Should the model fit be insufficient, the period adjusted sign test (as described by Senn[2]) will be used to estimate the effect of the intervention on the primary outcome.

Results will be presented as mean differences with 95% confidence intervals (if a mixed effects model is used, these will be adjusted for period effect) or as median differences with 95% confidence interval using the binomial method (if sign rank test is used, presented median differences will be unadjusted for period effect, as these cannot be derived from period adjusted sign test).

Due to an immediate effect of closed loop and the short half life of insulin, no carry-over effect of the intervention on the primary outcome is expected. Nonetheless, the first month of each stage will not be included in the analysis in order to wash-out any residual carry over effect. As the test for carry over effect has been shown to be flawed[3], no carry over test will be performed.

The statistical analysis plan reported in the study protocol differs to the one presented here. In the protocol, a 2 step procedure evaluating carry-over and period effect prior to superiority analysis using paired t-test was planned. After an updated review of the literature, it has been decided to follow current recommendations for analysis of cross-over studies using mixed effects model. This type of model accounts for the correlation within the participants and allows adjustment for a period effect which increases the power of the study (which is not possible using paired t-test).

3.10.2 ADJUSTED ANALYSES

No additional adjusted analysis will be performed.

3.10.3 SUBGROUP ANALYSES

Four subgroup analyses are planned by awareness of hypoglycaemia (based on Clark and Gold score) and fasting C-peptide levels at baseline. Stratified analysis for each subgroup will be performed.

3.10.4 TREATMENT OF MISSING DATA

Missing data will be quantified and patterns of missing data explored. Due to the nature of real time CGM, missing data are expected to be minimal.

Where the analysis is performed using mixed effects models, missing data will be handled by maximum likelihood approach within the model estimation.

Where non-parametric methods are used, due to a small sample size, missing data will be replaced using simple missing data imputation– replacing the missing value with the median of the stage.

3.10.5 OTHER SENSITIVITY ANALYSES

Sensitivity analysis with no adjustment for period effect will be performed and two per-protocol analyses.

3.11 ANALYSIS OF SECONDARY OUTCOMES

3.11.1 GLUCOSE OUTCOMES

All glucose outcomes are continuous outcomes. The analysis will follow the approach described above for the primary outcome. Sensitivity analysis without adjustment for period effect will be performed and using per-protocol populations. Same subgroup analysis as for primary outcome will be performed. Missing data will be treated the same as for main outcome.

3.11.2 CLINICAL OUTCOMES

Clinical outcomes include the safety outcomes and are a mixture of continuous, ordinal and count data. For continuous data, the analysis will follow the approach described above for the primary outcome. The period adjusted sign-rank test will be used for ordinal data. Count outcomes will be analysed using conditional negative binomial regression with exposure (number of months) included as an offset and adjusted for period effect. Sensitivity analysis will not adjust for period effect and using per protocol populations. Missing data will be treated the same as for main outcome. If missing data contains >50% of observations (missing due to remote visits), no intention-to-treat analysis will be performed and only per protocol analysis will be performed.

3.11.3 COGNITIVE FUNCTIONING

Cognitive functioning outcomes are continuous and binary outcomes. The analysis will follow the approach described above for the primary outcome and conditional logistic regression for binary outcomes, both adjusted for period effect. Sensitivity analysis will include no adjustment for period effect. Missing data will be treated the same as for main outcome. If missing data contains >50% of observations (missing due to remote visits), no intention-to-treat analysis will be performed and only per protocol analysis will be performed.

3.11.4 PSYCHOSOCIAL WELL-BEING AND SLEEP QUALITY (SUBJECTIVE)

Self-reported psychosocial well-being and sleep quality questionnaire outcomes are a mixture of continuous and ordinal outcomes. Continuous data will be analysed following the approach described above for the primary outcome. The sign-rank test will be used for ordinal data. Sensitivity analysis will include no adjustment for period effect. Missing data will be treated the same as for main outcome. If missing data contains >50% of observations (missing due to remote visits), no intention-to-treat analysis will be performed and only per protocol analysis will be performed.

3.11.5 SLEEP

Glucose outcomes for periods of sleep will be analysed as detailed for the primary outcome. Sleep onset and offset times are estimated by a wrist-worn actigraphy device. Sleep diaries are used to control the quality of the actigraphy data by removal of artefacts (e.g., device removal). Three continuous sleep metrics: sleep duration, sleep-efficiency (total sleep time / time in bed), and sleep latency (time between attempting to sleep and the beginning of sleep) will be compared between closed and open loop stages. The analysis will follow the approach described above for the primary outcome Sensitivity analysis will include no adjustment for period effect. If a sleep period has less than 70% of valid CGM readings it will be considered as missing data and treated the same as for the main outcome.

3.12 ANALYSIS OF SAFETY OUTCOMES

3.12.1 ADVERSE EVENTS

Number of adverse events, number of patients with at least one adverse event and incidence of events/100 person-years will be presented overall and for each adverse event type.

Conditional negative binomial regression will be used to compare number of events between the stages with the number of follow-up years as an offset.

3.13 ANALYSIS OF TERTIARY OUTCOMES

Tertiary outcomes will be analysed same as primary outcome. CL system performance outcomes that are applicable only to CL stage will be presented as median (inter-quartile range).

4. REFERENCES

1. Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G, Bonner-Weir S, King GL. Residual insulin production and pancreatic ß-cell turnover after 50 years of diabetes: Joslin Medalist Study. Diabetes. 2010 Nov;59(11):2846-53. doi: 10.2337/db10-0676. Epub 2010 Aug 10. PMID: 20699420; PMCID: PMC2963543.
2. Freeman PR. The performance of the two-stage analysis of two- treatment, two-period crossover trials. Stat Med 1989;8:1421-32. doi:10.1002/sim.4780081202
3. Senn S. Crossover-trials in Clinical Research. 2nd ed. Wiley, 2002. doi:10.1002/0470854596.

APPENDIX 1: PROPOSED TABLES AND FIGURES

Proposed figures

Trial flowchart
Plot of median glucose by time of day within each stage (5-minutely glucose measurements)
Plot of the difference in median glucose between stages by time of day (5-minutely glucose measurements)
Proportion of time in target range, above target range and below target range by hour of day within each stage
Forest plot for subgroup analysis of primary and secondary glucose outcomes

Proposed tables

Baseline characteristics (overall and per randomisation arms)
Compliance to intervention
Compliance to protocol and distribution of remote visits (overall and by site)
Analysis of primary and secondary glucose outcomes
Analysis of clinical outcomes
Analysis of cognitive functioning
Analysis of psychosocial well-being and self-reported sleep quality
Analysis of sleep outcomes
Adverse event