Statistical Analysis Plan

TRIAL FULL TITLE	Can flash glucose monitoring improve blood glucose levels in Indigenous Australians with type 2 diabetes?
TRIAL SHORT TITLE	FLASH pilot
TRIAL REGISTRATION	ACTRN12621000021875
TRIAL CHIEF INVESTIGATOR	A/Prof Elif Ekinci, Austin Health
PROTOCOL VERSION	Protocol No 1 Version 6 (10 December 2019)
TRIAL STATISTICIAN (S)	Ms Sabine Braat, University of Melbourne Dr Digsu Koye, University of Melbourne
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SAP VERSION	2.0
SAP VERSION DATE	16-JAN-2025

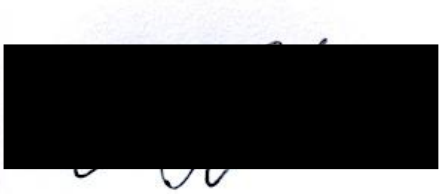
SAP Revision History

Version	Reason(s) for change	Date
1.0	Initial version before database lock	08-SEP-2022
2.0	Version after review by Journal Pilot and Feasibility Studies	16-JAN-2025

SAP Signatures

I give my approval for the attached SAP entitled FLASH pilot dated 16-JAN-2025.

Chief Investigator

Name / Affiliation	Signature	Date
A/Prof Elif Ekinci, Austin Health		16th January 2025

Trial Statistician

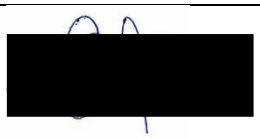
Name / Affiliation	Signature	Date
Dr Digsu Koye, University of Melbourne		16th January 2025

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Table of Contents

Abbreviations and Definitions

ABBREVIATION	DEFINITION
AE	Adverse Event
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DPP4	Dipeptidyl peptidase-4 inhibitor
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated haemoglobin
IMP	Investigational Medical Product
ITT	Intention-to-treat
LDA	Longitudinal data analysis
MAR	Missing at random
MISCH	Methods and implementation support for clinical and health research hub
RCT	Randomised Control Trial
SAP	Statistical Analysis Plan
SGLT2	Sodium-glucose cotransporter-2 inhibitors
SD	Standard deviation
SMBG	Self-monitored blood glucose

1 Introduction

1.1 Preface

Diabetes is a significant contributor to the mortality gap between Indigenous and non-Indigenous Australians. High blood glucose levels in Indigenous Australians are the leading driver of diabetes complications, which significantly increases the risk of chronic kidney disease, blindness and cardiovascular disease. In non-Indigenous populations with diabetes, knowledge gained from continuously monitoring of blood glucose levels has led to behavioural change and a reduction in blood glucose levels. However, this has never been studied in Indigenous Australians. There is an urgent need to find effective ways of improving blood glucose control in Indigenous population.

The FLASH study is a prospective, non-masked, individually randomised controlled pilot study of flash glucose monitoring over a 6-month period in Indigenous Australians with type 2 diabetes. 40 volunteers will be randomly assigned to either blood glucose monitoring by flash glucose monitoring (Abbott Freestyle Libre) or conventional self-monitored blood glucose (SMBG).

1.2 Purpose of the analyses

The purpose of this SAP is to outline the pre-planned analyses to be completed to support the main publication of the FLASH pilot study. Versions of the SAP will be tracked until unblinding of trial statistician/s and thereafter, with a clear distinction between the changes before and after unblinding. Any analyses not identified in the SAP after unblinding of the randomised study device will be clearly identified as such in the main publication and will be considered post-hoc.

2 Study Objectives and Endpoints

2.1 Study Objectives

The aim of this pilot, randomised control trial is to assess the effectiveness, safety and quality of life of flash glucose monitoring (FlashGM) compared with conventional SMBG over a 6-month period in Indigenous Australians with type 2 diabetes. This study will also determine the feasibility of flash glucose monitoring in Indigenous Australian population with type 2 diabetes.

Primary effectiveness objective: To evaluate if FlashGM is superior to SMBG after 6 months in reducing HbA1c.

The **secondary effectiveness objectives** of this study are:
To evaluate if FlashGM is superior to SMBG at 6 months in

a) increasing percentage (%) of time spent in target blood glucose levels (4.0-10mmol/L)
b) reducing percentage (%) of time spent in low blood glucose levels (<3.9 mmol/L),
c) reducing percentage (%) of time spent in high blood glucose levels (>15.0 mmol/L) and

This will be measured through the use of a blinded sensor at baseline and at 6 months.

Safety objective

To determine the percentage of participants with at least one and number of severe hypoglycaemic events requiring 3rd party assistance in FlashGM compared to SMBG during the study.

Quality of life objective

To determine quality of life of FlashGM compared to SMBG, as measured by the EQ-5D-3L after 6 months.

Exploratory objectives are listed in Section 7.3.

2.2 Endpoints

The **primary effectiveness endpoint** of this study is change in HbA1c level from baseline to 6 months.

Secondary effectiveness endpoints are:

- change in percentage (%) of time spent in target blood glucose levels (4.0-10 mmol/L) from baseline to 6 months,
- change in percentage (%) of time spent in low blood glucose levels (<3.9 mmol/L) from baseline to 6 months,
- change in percentage (%) of time spent in high blood glucose levels (>15.0 mmol/L) from baseline to 6 months.

Safety endpoint:

- Number and percentage of participants with at least one and number of severe hypoglycaemic events requiring 3rd party assistance occurring between baseline and 6 months.

Quality of life endpoint:

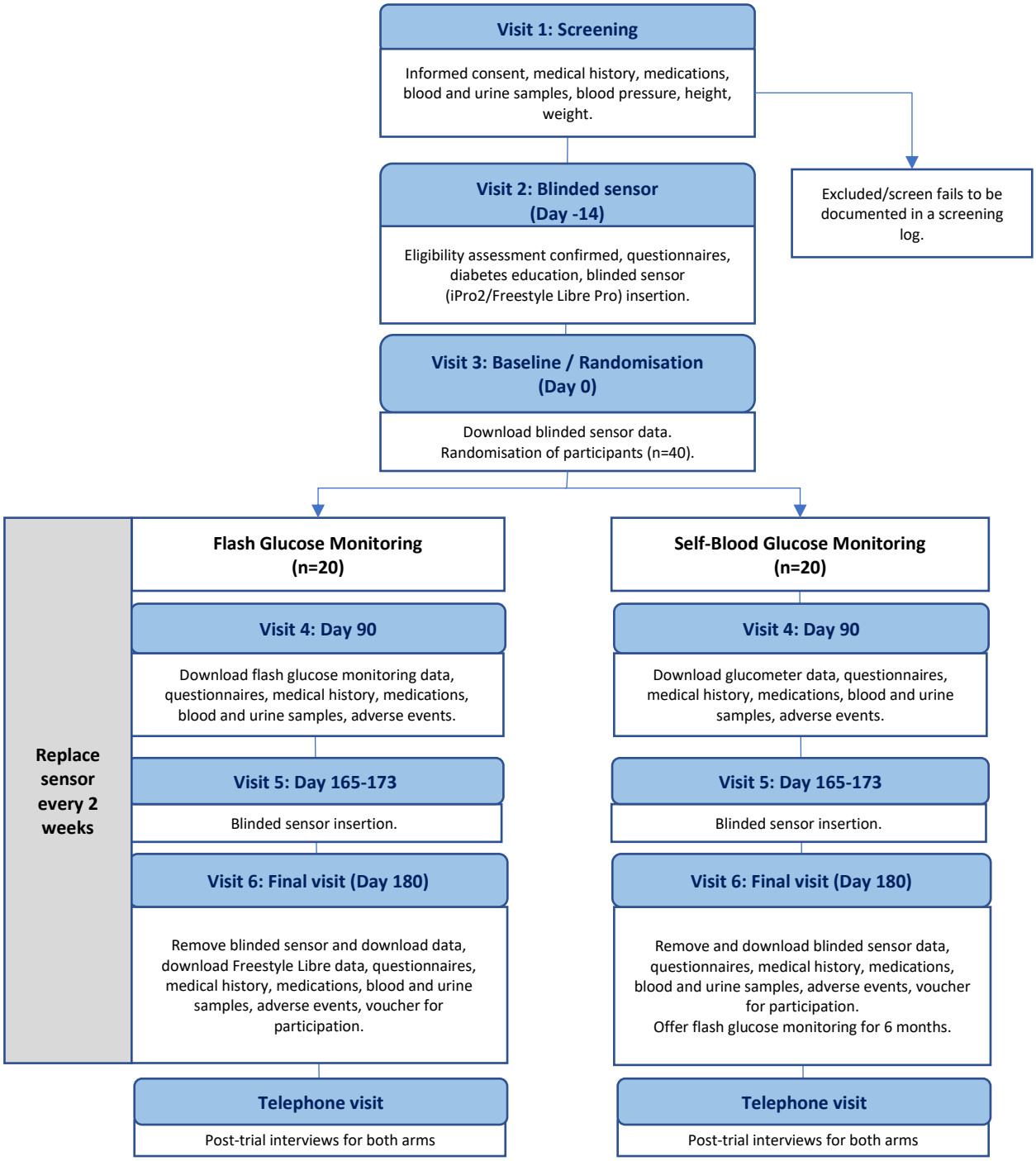
- Change in EQ-5D-3L score from baseline to 6 months.

3 Study Methods

3.1 Study Design and Plan

This study is a prospective, non-masked, individually randomised controlled pilot study of FlashGM compared with SMBG over a 6-month period in Indigenous Australians with type 2 diabetes.

Figure 1: Study design



3.2 Inclusion-Exclusion Criteria

Indigenous Australians with type 2 diabetes and high blood glucose levels, defined as a HbA1c $\geq$ 7.0% (on a recent blood test or at screening), and on injectable therapies will be included in this pilot study.

Treatment combinations for **inclusion**:

- Injectable therapy (including insulin) ± oral hypoglycaemia agent, or
- GLP-1 analogue (exenatide, liraglutide or dulaglutide) ± oral hypoglycaemic agents, or
- GLP-1 analogue and insulin ± oral hypoglycaemic agents

Participant's **exclusion** criteria:

- Age < 18 years
- Type 1 diabetes
- Active illicit drug use or heavy alcohol use (> 4 standard drinks/days)
- Active malignancy
- Known allergy to medical-grade adhesives
- On varying doses of corticosteroid therapy
- Using amphetamines, anabolic or weight-reducing medications

3.3 Randomisation and Blinding

Following written informed consent and baseline measurements, eligible individuals will be randomized to SMBG (control group) or FlashGM (intervention group) in a 1:1 ratio. The randomisation list will be computer-generated by an independent statistician using block randomisation and assignments will be sealed in sequentially numbered opaque envelopes by an independent support staff. Participants, investigators, and study staff cannot be masked to group allocation because of the nature of the intervention. The study statisticians will remain blinded until the database is clean, locked and ready for unblinding. Measures will be put in place to avoid accidental unblinding while the study is ongoing (e.g., not sharing outcomes that are revealing the treatment allocation).

3.4 Study Visit Schedule

Study variables will be collected according to the study visit schedule in Table 1.

Table 1 Study Visit Schedule

Standard Care Procedures	
Procedure	**Time / Visit**
Blinded sensor placement (Medtronic iPro2, Freestyle Libre PRO)	Day -7/14, 165/173 / (Week -1/-2, 23.5/24.5)
Blinded sensor removal	Day 0, 180 / (Week 0, 26)
HbA1c	Day 0, 90, 180 / (Week 0, 13, 26)
Fasting/random blood glucose	Day 0, 90, 180 / (Week 0, 13, 26)
Full blood examination (FBE)	Day 0, 90, 180 / (Week 0, 13, 26)

Urea, electrolytes & creatinine (UEC)	Day 0, 90, 180 / (Week 0, 13, 26)
Liver function test (LFT)	Day 0, 90, 180 / (Week 0, 13, 26)
Fasting/random lipid profile	Day 0, 90, 180 / (Week 0, 13, 26)
Urine albumin:creatinine ratio	Day 0, 90, 180 / (Week 0, 13, 26)
EQ-5D-3L questionnaire	Day 0, 180 / (Week 0, 26)
Medical History	Screening, Day 0
Medications	Screening, Day 0, 90, 180 / (Week 0, 13, 26)
Adverse Events	Day 0, 90, 167/173, 180 / (Week 0,13, 23.5/24.5, 26)

Time-windows will be used for converting visit dates into visit numbers according to the study visit schedule. Relative days will be derived as the visit date minus the randomisation date plus 1.

Table 2 Visit Windows

Visit	Target day	Lower limit (incl.)	Upper limit (incl.)
Visit 1 (Screening)	Day -14	Day -64	Day 0
Visit 2 (Confirmation of eligibility and Blinded sensor placement (Before randomisation))	Day -14	Day -64	Day 0
Visit 3 (Baseline and randomisation)	Day 0	Day -64	Day 0
Visit 4 (Month 3)	Day 90	Day 48	Day 132
Visit 5 (Blinded sensor placement (Before last visit))	Day 165*	Day 123	Day 215
Visit 6 (Month 6)	Day 180	Day 138	Day 264

* The Medtronic iPro2 device is worn for up to 7 days whereas the Abbott Freestyle Libre Pro is worn for 14 days.

Visit windows are set to be wide as there were several COVID-19 lockdowns during the conduct of the study where the Aboriginal Health Services were impacted. Assessments performed outside these visit windows will not be included in the analyses. If a study participant has more than one assessment done within the same

visit window, then the assessment closest to the target date will be used. The visit windows will be applied to the study variables described below in Section 3.5.

3.5 Study Variables

A detailed description of the effectiveness study variables is presented below. All safety study variables are detailed in Section 8.

3.5.1 HbA1c

HbA1c is glycosylated haemoglobin and reflects average glycaemia over the preceding 12 weeks. HbA1c in % and/or mmol/L will be collected from participants during routine blood test at baseline, 3 and 6 months. All HbA1c blood samples will be analysed in a NATA-accredited laboratory.

3.5.2 Time spent in target glucose, high or low glucose

Time spent in target blood glucose is the percentage of time that a person spends with their blood glucose levels between 4 and 10 mmol/L. It can be expressed as average hours per day or percentage (%) of readings (1). These data will be collected from the blinded sensor which is inserted pre-randomization (1 to 2 weeks before randomisation) for the baseline and day 165-173 (week 23.5-24.5) for end of follow-up assessment. The sensors will be worn for about 7-14 days.

Time spent in low glucose - the percentage of time that a person spends with their blood glucose levels <3.9 mmol/L.

Time spent in high glucose - the percentage of time that a person spends with their blood glucose levels >15mmol/L.

Percentage of time spent in target glucose range, high or low blood glucose values were calculated from the downloaded CSV files using a Stata program that was developed by our team. The results from our program were comparable with an R package called *GLU* (2). The reason we used our own program is because GLU considers complete days approach, it uses only days with complete 24 hour sensor glucose values to derive the percentage of time spent in target, low or high glucose levels.

Participants should have at least four days of blinded sensor data to calculate the above secondary endpoints. If a participant has less than four days of sensor data, the data will be excluded from the analyses.

In this study, two different blinded senor devices were used: Medtronic iPro2 and Abbott Freestyle Libre Pro. The need for the two devices was because we were not able to secure Abbot Freestyle Libre Pro from the outset of the trial. We had to start with the Medtronic iPro2 which was impractical in this setting. We then swapped across to the Abbott Freestyle Libre Pro for the duration of the study. The Medtronic iPro2 device is worn for up to 7 days whereas the Abbott Freestyle Libre Pro is worn for 14 days. The two devices use different algorithms to calculate time in glucose range. For the purpose of the pilot study, we will report findings by device (Abbott Freestyle Libre Pro or Medtronic iPro2). Each participant used only the one device.

3.5.3 EQ-5D-3L

The EQ-5D-3L questionnaire comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. EQ-5D-3L index values will be computed using the Australian value set developed by Viney *et. al.* (3).

3.6 Data Collection

A study investigator will record the participant's medical history, medication list, and record their physical observations at baseline, 3 and 6 months. At each visit, weight will be recorded on a calibrated scale; blood pressure and heart rate will be measured in a sitting position after 5 minutes of rest using an automated blood pressure monitor.

At baseline, 3 and 6 months, routine blood tests for HbA1c, fasting/random glucose, fasting/random lipid profile, FBE, UEC, LFT and urine albumin:creatinine ratio will be sought from participants' usual primary care provider. If these are not available, these tests will be collected at the study visit.

4 Sample Size

For this pilot study, 40 participants will be randomised to either flash glucose monitoring or SMBG, with 20 participants in each arm. The reason for this sample size is because of limitations of funding. However, a sample size of 12 per group has been shown to provide precision about the mean and variance (4).

5 General Considerations

5.1 Timing of Analyses

Study data entered and stored in the REDCap study database hosted by the University of Melbourne will be transferred to the trial biostatisticians located at the Centre for Epidemiology and Biostatistics at the University of Melbourne, Melbourne, Australia. After the last subject has concluded study participation, all study data are available, and all study data have been cleaned, a blinded review meeting will be held with the study chief investigators, trial and senior statisticians and study data manager (Audrey Eer) prior to database lock (defined as the state is kept constant, i.e., it is locked so that data cannot be subsequently amended). During this blinded data review meeting, the following topics will be discussed and decided upon without knowledge of the underlying randomisation order:

- Study participants who have withdrawn consent, in relation to the use of the Study participant's data (or part of it) in any of the analyses (Section 5.2). Data will be used up to the withdrawal of consent.
- Subjects with protocol violations as defined in Section 5.2.2, in relation to reporting on these participants.
- Inclusion or exclusion status of data with regards to the visit windows (Table 2 above).

After database lock, the randomised treatment allocation will be obtained from the independent statistician who generated the randomisation code and added to the study database by trial biostatisticians. This list will be compared with actual randomised assignment as documented in the REDCap database to look for any deviations from the planned randomisation (e.g., "as-randomised" versus "as-treated").

No database may be locked, random code unblinded, or analyses completed until the SAP has been approved (in case of updates since its initial approval). The planned analyses in this SAP will be conducted after unblinding of the database and any changes to this SAP after unblinding will be documented in an amendment of this SAP and considered post-hoc analyses.

5.2 Analysis Populations

Study participants will be reported and analysed according to their randomised treatment group ("as-randomised") for the intention-to-treat population and actual

treatment group ("as-treated") for the safety population. The following analysis populations are planned.

5.2.1 Intention-To-Treat Population

This will consist of all study participants who were randomised, excluding study participants who have withdrawn informed consent for use of all their data as documented in the minutes of the blinded data review meeting. This population will be used in the analysis of the primary and secondary effectiveness and quality of life outcome variables described in Section 3.5.

5.2.2 Per Protocol Population

No Per Protocol Population will be derived. Instead, we will report on participants with:

- A protocol violation is defined as no informed consent or violating in/exclusion criteria and will be documented in the minutes of the blinded data review meeting.

5.2.3 Safety Population

This will consist of all study participants who worn the Flash glucose monitor at least once (including controls), excluding study participants who have withdrawn informed consent for use of all their data as documented in the minutes of the blinded data review meeting. This population will be used in the analysis of the safety study variables.

5.3 Covariates and Subgroups

5.3.1 Covariates

The randomisation does not involve any stratification factors and the primary analysis model will not be adjusted for any covariates. This model will be referred to as the unadjusted model. We considered to fit an adjusted model for site, but there were not adequate number of participants at the Austin Health and Goulburn Valley Health.

5.3.2 Subgroups

No subgroup analysis is planned for this study.

5.4 Missing Data

To describe the missing data for the primary and secondary effectiveness study variables, the frequency and percentage of study participants with missing data at baseline, 3- and 6-months post-randomisation will be summarised for all study

variables in Section 3.5 overall and by treatment group for the intention-to-treat population. Where available, reasons for missingness will be tabulated.

As the primary strategy to handle missing data, the unadjusted analysis of the primary effectiveness study variable will use a likelihood-based approach as the primary approach to deal with missing data (i.e., longitudinal data analysis model (LDA)). Further details are provided in Section 7. This approach assumes that the probability of missing data on the study variable is not related to the missing data but to some of the observed measured data in the model. That is, it assumes that the data are Missing at Random (MAR). The model provides valid inference in the presence of missing data if the missing data mechanism is ignorable (i.e., missing completely at random (MCAR) or MAR).

5.5 Interim Analyses and Data Monitoring

No interim analysis is planned for this study.

5.6 Multi-centre Studies

Flash Pilot study is a multi-site study with participants recruited from three sites in Australia (Rumbalara Aboriginal Co-operative, Austin Health and Goulburn Valley Health). However, the study did not aim to recruit equal number of participants from each site. The primary effectiveness study variable will be analysed for all sites combined without adjustment for site in the models.

5.7 Multiple Testing

Statistical ~~testing~~ inference is planned for the primary effectiveness outcome only. ~~The null hypothesis of no difference between FlashGM and SMGB on HbA1c at 6 months will be evaluated at the two-sided 5% level of significance.~~ Two-sided 95% confidence intervals will be reported ~~alongside two-sided P-Values~~. Descriptive summary statistics by treatment group will be reported for the secondary, safety and quality of life outcomes.

6 Summary of Study Data

6.1 Subject Disposition

The flow of participants will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram and is presented in Figure 1 in the Appendix.

We will report the following:

- Number of participants assessed for eligibility
- Number of participants excluded due to not meeting the inclusion criteria, meeting the exclusion criteria, declined to participate and other reasons
- Number of participants randomised/allocated to the FlashGM and SMBG.
- Number of participants completed the 3-month follow-up for the primary effectiveness outcome and the number of participants who withdrew from the study or lost to follow-up, including reasons.
- Number of participants completed the 6-month follow-up for the primary effectiveness outcome and the number of participants who withdrew from the study or lost to follow-up, including reasons.

Feasibility outcomes include drop-out/ completion rate and recruitment rate. The number and proportion of participants will be reported alongside a two-sided 95% confidence interval for the proportion using the Clopper-Pearson method.

6.2 Demographic and Baseline Variables

Demographic and baseline variables will be summarised and presented by treatment group (Flash GM, SMBG) using frequencies and percentages for categorical variables, mean and standard deviation for continuous variables, or median and quartiles (25th and 75th percentile) for non-symmetrical continuous variables. If variables have missing values, we will report the non-missing sample either in the table or in the footnote of the table.

We will present the demographic data as per Table 1 in the Appendix.

6.3 Concurrent Illnesses and Medical Conditions

Participants were instructed to inform the study investigators of the details of any concurrent illnesses and medical conditions. All concurrent illnesses and medical conditions details were recorded on the CRF.

We will report this as part of Table 1 in the Appendix.

6.4 Prior and Concurrent Medications

Participants were instructed to inform the study investigators of the details (indication, dose, dates of administration) of their medication consumption during the course of the study. All current and new concomitant medication details were recorded on the CRF. Diabetes and relevant cardiovascular medications of interest were coded according to their classes.

We will report the proportion of patients on diabetes and cardiovascular medications at baseline (i.e., reported before randomisation) as part of Table 1 in the Appendix, and proportion of participants on Insulin, total daily dose of insulin and the proportion of participants on one or more glucose lowering medications at baseline, 3 and 6 months will be reported as part of the exploratory analysis (Section 7.3).

6.5 Treatment Compliance

Treatment compliance was not assessed in this pilot study.

7 Effectiveness Analyses

For all effectiveness analyses, we will use the following principles:

- We will use the ITT population for all effectiveness analyses.
- Confidence intervals ~~and P-Values~~ will be presented following the multiple testing strategies described in Section 5.7.

7.1 Primary Effectiveness Analysis

The primary effectiveness study variable HbA1c will be analysed using a longitudinal data analysis (LDA) model, with response consisting of all values (baseline, 3- and 6-months) and the model including factors representing treatment group, time point, and treatment group by time interaction. The model will not be forced to assume a common baseline HbA1c mean across the two treatment arms due to the small sample size.

Given the small sample size, the LDA model will be fitted with methods that are known to perform well under small sample size and potential deviations from distributional assumptions such as the Restricted maximum likelihood (REML) estimation with the Kenward-Roger method to obtain the degrees of freedom (5).

The LDA model provides valid inference if the underlying missing data mechanism is MAR. The variance-covariance among the repeated measurements will be defined as

unstructured and in the case of non-convergence we will consider alternative structures. The primary hypothesis will be examined by obtaining an estimate and two-sided 95% CI of the absolute difference between the groups in change from baseline at 6 months.

7.2 Secondary Effectiveness Analyses

The following secondary outcomes will be treated as continuous outcomes, which will be summarised and presented by treatment group (Flash GM, SMBG), and within each treatment group by device (Abbott Freestyle Libro Pro, Medtronic iPro2) using mean and standard deviation for symmetrical variables, or median and quartiles (25th and 75th percentile) for non-symmetrical variables:

- change in percentage of time spent in target glucose (4.0-10 mmol/L)
- change in percentage of time spent in low glucose (<3.9 mmol/L)
- change in percentage of time spent in high glucose (>15.0 mmol/L)

All secondary effectiveness endpoints as well as exploratory objectives will not be compared using statistical tests.

7.3 Exploratory Effectiveness Analyses

The following exploratory outcomes will be treated as continuous outcomes, which will be summarised and presented by treatment group (Flash GM, SMBG) and device (Abbott Freestyle Libro Pro, Medtronic iPro2) using mean and standard deviation for symmetrical variables, or median and quartiles (25th and 75th percentile) for non-symmetrical variables:

- Change in percentage of time spent above target glucose (>13.9 mmol/L)
- Change in percentage of time spent above target glucose (10.1-13.9 mmol/L)
- Change in percentage of time spent in target glucose (3.9-10.0 mmol/L)
- Change in percentage of time spent below target glucose (3.0-3.8 mmol/L)
- Change in percentage of time spent below target glucose (<3.0 mmol/L)

Other exploratory analyses to report:

- Changes in insulin usage (for those who are recorded as using insulin at any timepoint in the study)
    - N (%) change in requirements for insulin usage from baseline to 6 months (i.e. the commencement or discontinuation of insulin)
    - Change in total daily dose (TDD) of insulin from baseline to 6 months

- Changes in number of glucose-lowering medications from baseline to 6 months

8 Safety Analyses

For all safety analyses, we will use the following principles:

- We will use the safety population for all safety analyses.
- Descriptive statistics (number and percentage) of participants with at least one adverse event will be reported by treatment group.
- We will not fit statistical models for the safety analysis.

8.1 Extent of Exposure

Time the device was worn by participants will be summarised for those randomised to the intervention group.

8.2 Adverse Events

MedDRA v25.0 was used to code adverse events. We will report the number and percentage of study participants with at least one adverse event and the number of events by treatment group.

The "preferred terms" were derived from the MedDRA dictionary from interpretation of all free-text descriptions of adverse events recorded during the trial. This interpretation was performed by one investigator (AE) when there was a single MedDRA pathway. However, where there was more than one MedDRA pathway, consensus was reached between two investigators (AE and EE).

8.3 Deaths, Serious Adverse Events and other Significant Adverse Events

We will report the number and percentage of study participants with at least one SAE between baseline and 6 months by treatment group with event defined as:

- Deaths
- Hospitalisations
- SAEs (include hospitalisation and death).

Other significant adverse events

- Severe hypoglycaemic events (requiring 3rd party assistance)
- Hospital admission
- Negative signs and symptoms related to glucose measurement.

8.4 Clinical Laboratory Evaluations

Summaries of laboratory findings (full blood examination, urea and electrolytes, liver function test, lipid and glucose profile, and urinalysis) will be reported as a supplementary table (Appendix 1).

9 Other Analyses

We will use the ITT population in the analysis of quality of life. The EQ-5D-3L data will be summarised by treatment groups using median and quartiles (25th and 75th percentile) using the Australian value set developed by Rosalie Viney (3). Post-trial qualitative interview data will be analysed using appropriate qualitative analysis methods. There is no further analysis planned for this data.

10 Technical Details

Analysis will be conducted using Stata/SE for Windows version 17.0 (64-bit x86-64) or higher. We will report the software and version used at the time of reporting.

11 Validation of Output

The analysis of the primary outcome variable (Section 7.1) will be programmed independently by the senior statistician. Discrepancies will be discussed and resolved by consensus. All other analyses will be conducted by the trial statistician only and reviewed by the senior statistician.

12 Summary of Changes to the Registry and Protocol

Changes compared to registry:

- The registry states that participants will wear the Flash Libre Pro as the blinded sensor for 2 weeks prior to randomisation and 2 weeks prior to completion of the study. This trial was registered retrospectively after the trial had commenced. The first 19 participants used the Medtronic iPro2 as the blinded sensor and this was worn for 7 days prior to randomisation and 7 days prior

to completion of the study. The remaining 21 participants wore the Freestyle Libre Pro as the blinded sensor 2 weeks prior to randomisation and 2 weeks prior to completion of the study. The Abbott Freestyle Libre Pro is a professional blinded flash glucose monitoring system whereas the Medtronic iPro2 is a blinded continuous glucose monitoring system.

- Cost-effectiveness analysis using EQ-5D was specified as a secondary outcome in the trial registration. However, due to the small sample size, quality of life will be analysed using the EQ-5D-3L (3L had not been specified in the trial registration).
- Goulburn Valley Health is the only listed recruitment hospital. Recruitment sites for this pilot study included Rumbalara Aboriginal Co-operative, Goulburn Valley Health and Austin Heath.

Changes compared to protocol:

- Protocol states planned participant recruitment was 24, but this was increased to 40.
- Due of the sample size, missing data and change in blinded sensor device, not all the proposed analyses in the protocol will be done. A statistical model will be fitted for the primary outcome variable only; all secondary and exploratory outcomes will be described using summary measures.
- Cost-effectiveness analysis using EQ-5D was specified as a secondary outcome in the trial protocol. However, due to the small sample size, quality of life will be analysed using the EQ-5D-3L (3L had not been specified in the trial protocol).
- For this pilot study, Rumbalara Aboriginal Co-operative is the only study site that has been listed. This was extended to include Goulburn Valley Health and Austin Health (these sites were not listed in the participating study sites in the study design).
- The study protocol consort diagram (Figure 4 in protocol version 6) reflects the anticipated number of participants required in the NHMRC multicentre study rather than this pilot study, where we aimed to recruit 40 participants.

- The "standard care procedures" table (Table 1) in the SAP (section 3.4 study visit schedule) has 4 additional rows to include: EQ-5D-3L questionnaire, Medical history, Medications, Adverse events.

13 Summary of Changes to the Statistical Analysis Plan

Changes to the version of the SAP prior to unblinding have been marked in red.

- Clarified the analysis of the feasibility outcomes in Section 6.1.
- Removed P-values for HbA1c in Section 5.7, Section 7 and Table 2.

14 References

1. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-1603.

2. Millard LAC, Patel N, Tilling K, et al. GLU: a software package for analysing continuously measured glucose levels in epidemiology, International Journal of Epidemiology, Volume 49, Issue 3, 2020, Pages 744-757.

3. Viney R, Norman R, King MT et al. Time trade-off derived EQ-5D weights for Australia. Value Health. 2011;14(6):928-36.

4. Julious, S., Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics, 2005. 4(4): p. 287-291.

5. McNeish D. Small Sample Methods for Multilevel Modeling: A Colloquial Elucidation of REML and the Kenward-Roger Correction. Multivariate Behav Res. 2017;52(5):661-670.

15 Listing of Key Tables and Figures

Title	Number	Population
The CONSORT flow chart	Figure 1	NA
Key Baseline Demographic and Clinical Characteristics of Participants and Medications by Treatment Group	Table 1	ITT
Primary, Safety, and Quality of Life Outcomes by Treatment Group	Table 2	ITT/Safety
Secondary Outcomes by Treatment Group and Device	Table 3	ITT
Number (%) of Participants with at least one Adverse Event by Treatment Group	Table 4	Safety
Exploratory Effectiveness Outcomes by Treatment Group and Device	Table 5	ITT
Insulin and Other Glucose Lowering Medications use by Treatment Group	Table 6	ITT
Clinical Laboratory Evaluations	Table 7	Safety

NA = Not Applicable, ITT = Intention-To-Treat

Depending on the journal, some of the tables will be placed as a Supplementary Table.

Figure 1 – The CONSORT flow chart

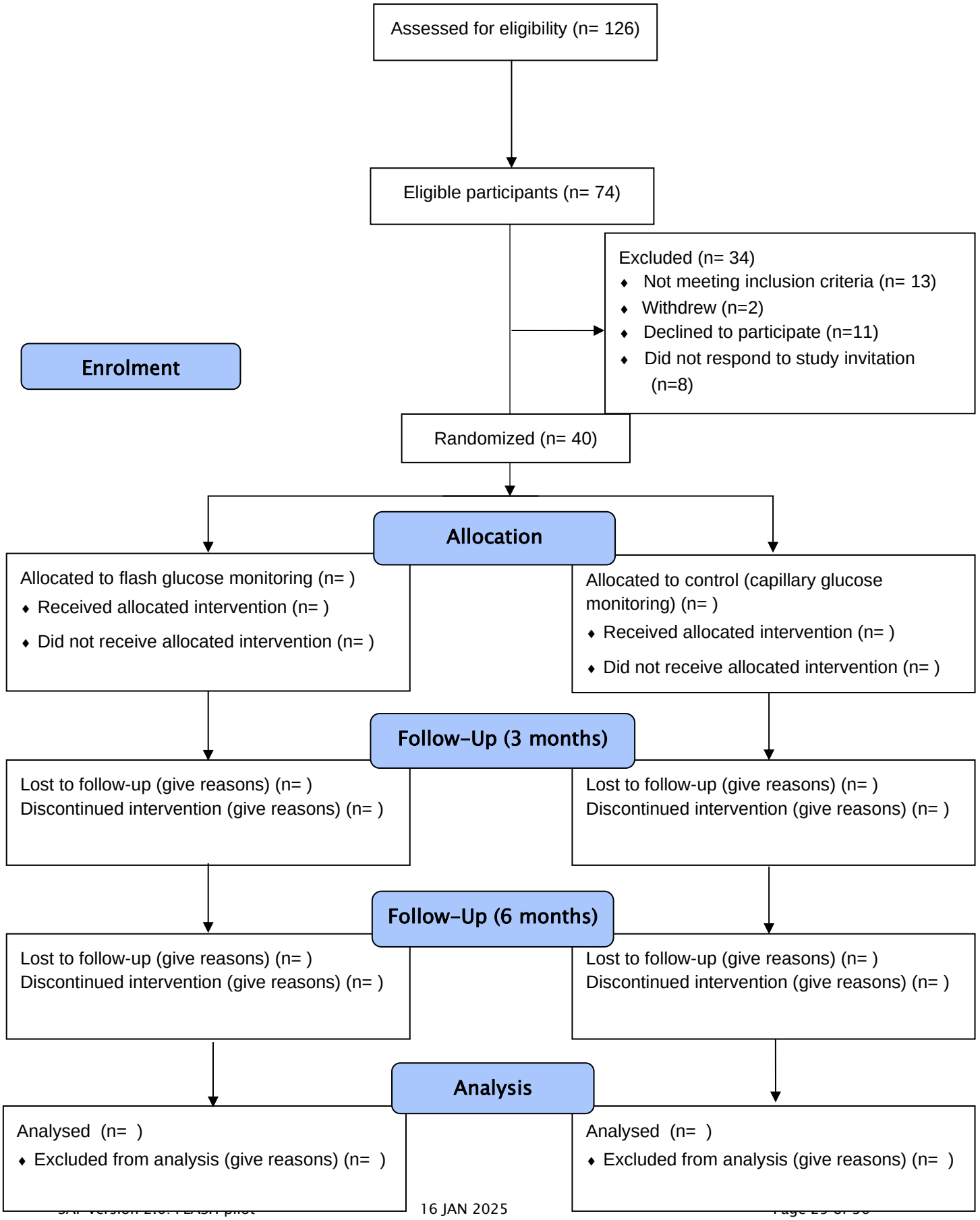


Table 1 - Key Baseline Demographic and Clinical Characteristics of Participants and Medications by treatment group

Characteristic	Flash glucose monitoring N=XX	Self-monitored blood glucose N=XX
Age (years), Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Female sex, n (%)	xx (x%)	xx (x%)
Glycated haemoglobin (%), Mean (SD)	x.x (x.x)	x.x (x.x)
Body Mass Index, Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Systolic blood pressure (mmHg), Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Diastolic blood pressure (mmHg), Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Diabetes duration (years), Median (IQR)	xx.x (xx.x-x.x)	xx.x (xx.x-x.x)
Significant medical history, n (%)		
Stroke or transient ischaemic attack	xx (x%)	xx (x%)
Ischaemic heart disease	xx (x%)	xx (x%)
Heart failure	xx (x%)	xx (x%)
Peripheral vascular disease	xx (x%)	xx (x%)
Retinopathy	xx (x%)	xx (x%)
Chronic kidney disease	xx (x%)	xx (x%)
Peripheral neuropathy	xx (x%)	xx (x%)
Total cholesterol (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)
Triglycerides (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)
LDL-C (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)
Creatinine (umol/L), Median (IQR)	xx.x (xx.x-x.x)	xx.x (xx.x-xx.x)
Estimated glomerular filtration rate (ml/min/1.73m^2), n (%)		
≥ 60 (ml/min/1.73m^2)	xx (x%)	xx (x%)
45 - <60 (ml/min/1.73m^2)	xx (x%)	xx (x%)
25- <45 (ml/min/1.73m^2)	xx (x%)	xx (x%)
<25 (ml/min/1.73m^2)	xx (x%)	xx (x%)
Urine Albumin-to-Creatinine ratio (mg/mmmol creatinine), n (%)		
<30 (mg/mmol)	xx (x%)	xx (x%)
30 to <300 (mg/mmol)	xx (x%)	xx (x%)
≥ 300 (mg/mmol)	xx (x%)	xx (x%)
Medications, n (%)		
Antiplatelet	xx (x%)	xx (x%)
Renin-angiotensin system inhibitor	xx (x%)	xx (x%)
HMG-CoA reductase inhibitor	xx (x%)	xx (x%)
Glucose-lowering therapy	xx (x%)	xx (x%)

Insulin	xx (x%)	xx (x%)
Metformin	xx (x%)	xx (x%)
Sulphonylurea	xx (x%)	xx (x%)
SGLT2 inhibitor	xx (x%)	xx (x%)
GLP-1 receptor agonist	xx (x%)	xx (x%)
DPP4 inhibitor	xx (x%)	xx (x%)
Thiazolidinediones	xx (x%)	xx (x%)
Alpha-glucosidase inhibitors	xx (x%)	xx (x%)

SD = Standard Deviation, IQR = 25th to 75th percentile, LDL-C = Low density lipoprotein cholesterol, SGLT2 = Sodium-glucose co-transporter-2 inhibitor, GLP-1 = Glucagon-like peptide 1 agonists, DPP4 = Dipeptidyl peptidase 4 inhibitors.

Table 2 – Primary, Safety and Quality of Life Outcomes by Treatment Group (Intention-to-Treat/Safety Population)

Outcome	Flash glucose monitoring N=XX	Self-monitored blood glucose N=XX	Mean difference (95% CI)
Primary effectiveness outcome, mean (SD)			
HbA1c (%)			
Baseline	x.x (x.x)	x.x (x.x)	
3 months	x.x (x.x)	x.x (x.x)	x.xx (x.xx-x.xx)*
6 months	x.x (x.x)	x.x (x.x)	x.xx (x.xx-x.xx)**
HbA1c (mmol/mol)			
Baseline	xx.x (xx.x)	xx.x (xx.x)	
3 months	xx.x (xx.x)	xx.x (xx.x)	x.xx (x.xx-x.xx)*
6 months	xx.x (xx.x)	xx.x (xx.x)	x.xx (x.xx-x.xx)**
Safety outcome, n (%)			
Severe hypoglycaemic events requiring 3rd party assistance			
Baseline	x (x.x%)	x (x.x%)	-
6 months	x (x.x%)	x (x.x%)	-
Quality of Life outcome, median (IQR)			
EQ-5D-3L score			
Baseline	x.x (x.x-x.x)	x.x (x.x-x.x)	-
6 months	x.x (x.x-x.x)	x.x (x.x-x.x)	-

n (%) = number and percentage of participants with at least one event. SD = Standard Deviation, IQR = 25th to 75th percentile, CI = Confidence Interval *EQ-5D-3L* = EuroQol 5-Dimension 3-Level (0-1).

~~*P-value = x.xxx; ** P-value = x.xxx~~

Table 3 – Secondary Outcomes by Treatment Group and Device (Intention-to-Treat Population)

Outcome	Flash glucose monitoring		Self-monitored blood glucose	
	Freestyle Libre Pro N=XX	iPro2 N=XX	Freestyle Libre Pro N=XX	iPro2 N=XX
Percentage time in target glucose (4 – 10 mmol/L)				
Baseline	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
6 months	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
Percentage time in low glucose (<3.9 mmol/L)				
Baseline	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
6 months	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
Percentage time in high glucose (>15 mmol/L)				
Baseline	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
6 months	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)

Data are presented as median (25^{th} to 75^{th} percentile)

Table 4 – Number (%) of participants with at least one Adverse Event by Treatment Group (Safety Population)

	Flash glucose monitoring N=XX	Self-monitored blood glucose N=XX
Adverse events	X (X.X%) [X]	X (X.X%) [X]
Serious adverse events	X (X.X%) [X]	X (X.X%) [X]
Device-related adverse events	X (X.X%) [X]	X (X.X%) [X]
Hospitalization	X (X.X%) [X]	X (X.X%) [X]
Death	X (X.X%)	X (X.X%)

Note: n (%) = number and percentage of participants with at least one event. [N] = number of events.

Table 5 – Exploratory Effectiveness Outcomes by Treatment Group and Device (Intention-to-Treat Population)

Outcome	Flash glucose monitoring		Self-monitored blood glucose	
	Freestyle Libre Pro N=XX	iPro2 N=XX	Freestyle Libre Pro N=XX	iPro2 N=XX
Percentage time in very high glucose (>13.9mmol/L)				
Baseline	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
6 months	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
Percentage time in high glucose (10.1–13.9 mmol/L)				
Baseline	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
6 months	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
Percentage time in target glucose (3.9–10 mmol/L)				
Baseline	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
6 months	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)	xx.x (xx.x–xx.x)
Percentage time in low glucose (3.0–3.8 mmol/L)				
Baseline	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
6 months	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
Percentage time in very low glucose (<3.0mmol/L)				
Baseline	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
6 months	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)

Data are presented as median (25th to 75th percentile)

Table 6 – Insulin and other glucose lowering medications use by Treatment Group (Intention-to-Treat Population)

	Flash glucose monitoring N=XX	Self-monitored blood glucose N=XX
Insulin use		
N (%)		
Baseline	X (X.X%)	X (X.X%)
3 months	X (X.X%)	X (X.X%)
6 months	X (X.X%)	X (X.X%)
Total daily dose, Median (IQR)		
Baseline	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
3 months	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
6 months	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
No. of non-insulin glucose lowering medication use		
Baseline, n (%)		
None	X (X.X%)	X (X.X%)
1	X (X.X%)	X (X.X%)
2	X (X.X%)	X (X.X%)
3	X (X.X%)	X (X.X%)
4		
3 months, n (%)		
None	X (X.X%)	X (X.X%)
1	X (X.X%)	X (X.X%)
2	X (X.X%)	X (X.X%)

3	X (X.X%)	X (X.X%)
4	X (X.X%)	X (X.X%)
6 months, n (%)		
None	X (X.X%)	X (X.X%)
1	X (X.X%)	X (X.X%)
2	X (X.X%)	X (X.X%)
3	X (X.X%)	X (X.X%)
4	X (X.X%)	X (X.X%)

IQR = 25th to 75th percentile

Table 7 – Clinical Laboratory Evaluations (Safety Population)

Outcome	Baseline		3 months		6 months	
	Flash glucose monitoring N=xx	Self-monitored blood glucose N=xx	Flash glucose monitoring N=xx	Self-monitored blood glucose N=xx	Flash glucose monitoring N=xx	Self-monitored blood glucose N=xx
Full blood examination						
Haemoglobin (g/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
White cell count (x10^9/L), Median (IQR)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)
Platelets (x10^9/L), Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Urea and Electrolytes						
Sodium (mmol/L), Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Potassium (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Chloride (mmol/L), Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)	xxx.x (xx.x)
Bicarbonate (mmol/L), Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
Urea (mmol/L), Median (IQR)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)	x.x (x.x–x.x)

Creatine (umol/L), Median (IQR)	x.x (x.x-x.x)	x.x (x.x-x.x)	x.x (x.x-x.x)	x.x (x.x-x.x)	x.x (x.x-x.x)	x.x (x.x-x.x)
eGFR (ml/min/1.73)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Liver Function Tests						
Bilirubin (umol/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Alkaline Phosphatase (U/L)), Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
Gamma-glutamyl transferase (U/L), Median (IQR)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Alanine transaminase (U/L), Median (IQR)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Protein (g/L), Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
Albumin (g/L), Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
Lipid profile						
Total cholesterol (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Triglycerides (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
LDL-C (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
HDL-C (mmol/L), Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Diabetes-related						

Glucose* (mmol/L), Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
Urine Albumin : Creatinine (mg/mmol creatinine), Median (IQR)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)

* Fasting or random glucose

SD = Standard Deviation, IQR = 25th to 75th percentile, LDL-C = Low density lipoprotein cholesterol, HDL-C = High density lipoprotein cholesterol.