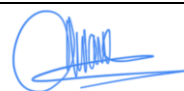


Statistical Analysis Plan

GlucoVITAL-1: Perioperative CGM measurement standards

Version 1.0

Date: 8th October 2024

Person(s) contributing to the analysis plan	
Name(s) and position(s)	Gareth Ackland (Chief Investigator) Nick Oliver (Co-Investigator) Sham Jhanji (Co-Investigator) Henrike Janssen (Co-Investigator) Priyanthi Dias (Study Manager)
Authorisation	
Position	Chief Investigator
Name	Gareth Ackland
Signature	
Date	8 th October 2024
Position	Trial Statistician
Name	Kamran Khan
Signature	
Date	8 th October 2024

1. Administrative information

Study Information

REC number	23/PR/0677
Study Sponsor	Queen Mary University of London
Study Sponsor reference	157967
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ISRCTN number	46862025
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Remit of the SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported for the GlucoVITAL study 1. It is important to set these out and to agree them in advance of inspecting the outcome data for the trial, so that data derived decisions in the analysis are avoided. Any exploratory, post hoc, or unplanned analysis will be clearly identified as such in the respective study analysis report.

Study design

Study objectives	Primary Objective Bland-Altman analysis at three pre-specified timepoints (before surgery, end of surgery and postoperative day 1) between DEXCOM G7 continuous glucose values and corresponding blood gas analyser glucose measurements. Secondary Objectives (before surgery, end of surgery and postoperative day 1, plus all paired glucose measurements in the first 24h after surgery) • % Mean Absolute Relative Difference (MARD) at three pre-specified timepoints (before surgery, end of surgery and postoperative day 1) • Surveillance error grids, including Parkes and Clarke Error Grids. • %15/15 (equivalent to ISO 15197 2013) and %20/20.
Study design	Observational analysis.
Setting	Surgical services of hospitals undertaking major elective surgery.
Participants	Inclusion criteria 1. Age $\geq$ 50 years 2. Elective major non-cardiac surgery under general anaesthesia 3. Written informed consent for trial participation Exclusion criteria 1. Known contraindication to either TIVA or inhalational anaesthesia 2. Clinician refusal 3. Participant not expected to survive for 30 days 4. Previous participation and completion in the GlucoVITAL trial 5. Inability to give informed consent/complete questionnaires.
Statistical treatise	Paired comparison analyses.
Primary outcome measure	Paired glucose measures from a minimum of three pre-specified timepoints (before surgery, end of surgery and postoperative day 1).
Sample size	Minimum of 110 paired sample comparisons.

2. Background

Automation of glucose measurements by continuous glucose monitoring (CGM) devices is now commonplace in surgical patients with diabetes mellitus. The latest generation DEXCOM G7 CGM device measures interstitial glucose every 5 minutes via an amperometric glucose oxidase method.¹ The seventh-generation G7 CGM system (Dexcom) provides several improvements over the previous G6 system, including better accuracy in nonpregnant adults, a simpler insertion process, a shorter warmup period, and is a smaller, thinner wearable. Continuous information about the current, predicted trajectory and rate of glucose change may help clinical care and reduce staff workload. However, hyperglycaemia has re-emerged as a pivotal player in acute perioperative organ injury in patients without established diabetes mellitus. Recent large observational cohort series have identified that substantial numbers of patients without an established diagnosis of diabetes mellitus experience undetected hyperglycaemia.² Alarming, non-diabetic individuals have twice the number of serious complications for the same level of hyperglycaemia sustained by patients with established diabetes mellitus. GlucoVISION identified that modest elevations in preoperative glucose concentration (fasting glucose of >6.4 mmol/L) were associated with a higher risk of developing postoperative cardiovascular outcomes, but particularly so in patients without diabetes mellitus.³ Thus, paradoxically, the vast majority of non-diabetic patients undergoing major surgery - even in more advanced healthcare settings - have hyperglycaemic periods that remain undetected.[3] The advent of CGM monitors that require far shorter periods for calibration before use means that this issue can be directly addressed in individuals without diabetes mellitus. However, before broader use, an understanding of the performance characteristics of the latest generation real-time continuous glucose monitoring systems during elective surgery is required.

3. Outcome measures

Primary outcome measure

- The primary outcome Systematic Measurement Difference (Bias) and 95% limits of agreement, calculated by Bland-Altman analysis.

Secondary outcome measures

(for each pre-specified timepoint and also overall paired glucose measurements for entire perioperative stay)

- % Mean Absolute Relative Difference (MARD) between blood gas analyser measurement of blood glucose and corresponding CGM data.⁴
- Error grids comprising the latest Diabetes Technology Society Error Grid,⁵ plus surveillance, Parkes, Clarke error grids to assess clinical accuracy and illustrate the clinical consequences of sensor/reference deviation.⁶ We will use nomenclature to report the proportion of readings that fall in clinically acceptable regions A and B, visualized through a scatterplot showing all five regions for each of these four error grid constructs.
- %15/15 (equivalent to ISO 15197 2013) and %20/20 measures of accuracy.⁷

Safety measures

- Usability metrics included sensor availability (proportion of available sensor measurements)
- Incidence of unplanned sensor replacement events.
- Adverse device effects.

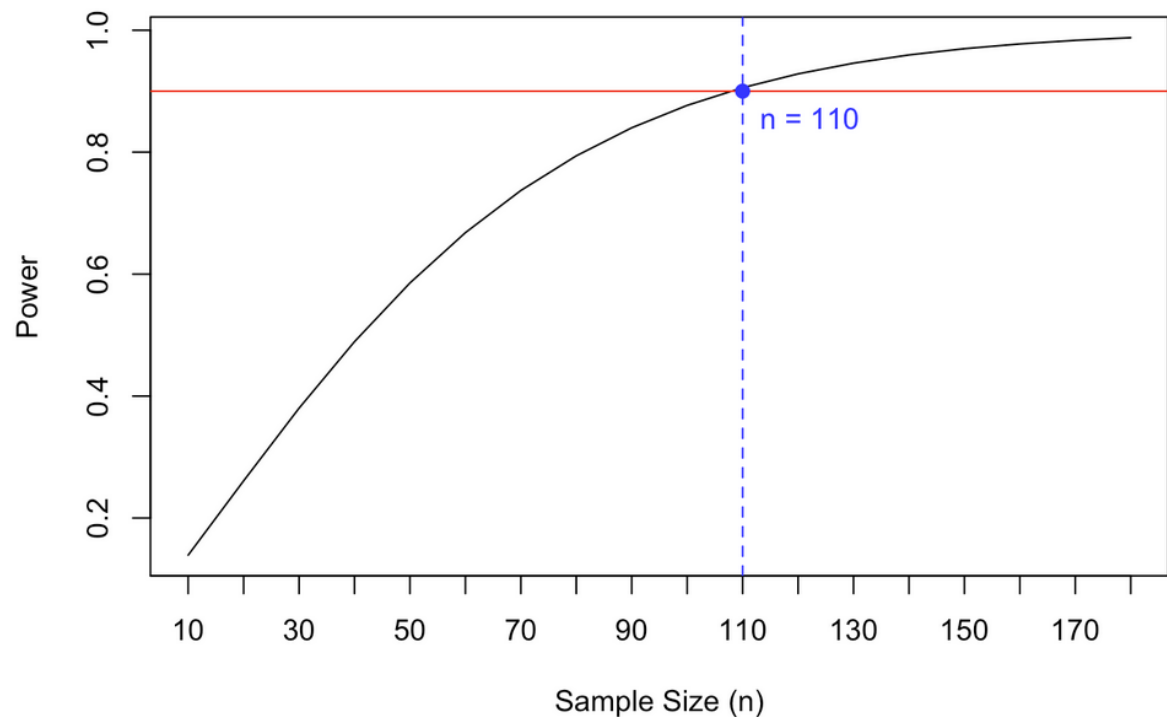
Pre-specified subgroup analysis

Measurements will be compared separately in individuals with type 2 diabetes mellitus.

Sample size calculation

The study would require a minimum sample size of 110 paired samples to achieve a power of 90% and a level of significance of 5% (two sided), for detecting a mean of the differences of 1 mmol.l⁻¹ between pairs, assuming the standard deviation of the differences to be 0.8 mmol.l⁻¹ and a clinically acceptable difference of 3mmol (limit of agreement).

Power Curve for Bland-Altman Sample Size Estimation



Randomisation procedure

As part of the VITAL study, participants would have been randomised on a 1:1 basis to receive either TIVA or inhalational anaesthesia, according to VITAL Protocol Version 1.0 (16th Jun 2021). The mode of anaesthesia will not be considered in this calibration analysis.

4. Analysis methods

Summary of participant characteristics

Preoperative characteristics will be summarised for participants with and without diabetes mellitus, summarised by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. The following baseline characteristics will be summarised by treatment group:

- Age (years)
- Gender (male/female)
- Co-morbid disease: COPD; asthma; interstitial lung disease/pulmonary fibrosis; ischaemic heart disease; heart failure; liver cirrhosis; active cancer; stroke/TIA; peripheral vascular disease; hypertension
- ASA grade
- Chronic treatment for diabetes mellitus.
- Surgical procedure performed: (a) surgery involving the gut; (b) all other surgery
- Cardiovascular medication: (a) beta-blocker; (b) calcium channel antagonist; (c) Doxazosin; (d) Diuretic; (e) Statin; (f) Nitrate; (g) Anti-platelet agents (h) ACE-I/ARB drugs

General analysis principles

Patients with missing paired outcome data will be excluded from the analysis but missing data will be reported. For the analysis of the primary outcome, each secondary outcome, and all process measures, we will present the following information:

- The number of patients included in each analysis, for each pre-specified timepoint (before surgery, end of surgery and postoperative day 1).
- A summary statistic of the outcome (e.g. mean (SD), number (%)).
- A 95% confidence interval for the estimated treatment effect
- A two-sided p-value; for all analyses, a significance level of 5% will be used.

Analysis software

All analyses will be conducted in R v4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and/or NCSS 2023 (NCSS 2023 Statistical Software (2023). NCSS, LLC. Kaysville, Utah, USA, [ncss.com/software/ncss](https://www.ncss.com/software/ncss))

Analysis of primary outcome

Primary analysis

- To quantify bias, “limits of agreement,” defined as $\text{mean} \pm 2 \times \text{standard deviation}$ (or, for normally distributed data, $\text{mean} \pm 1.96 \times \text{standard deviation}$), within which 95% of differences will be undertaken by Bland-Altman analysis and plotted by Bland-Altman plot.

Analysis of secondary outcomes

(including all paired glucose measurements in the first 24h after surgery, and entire perioperative stay)

- % Mean Absolute Relative Difference is the average of all individual pairs between CGM/blood gas measurement results and corresponding comparison method results within a given study. % Mean Absolute Relative Difference (MARD) between blood gas analyser measurement of blood glucose and corresponding CGM data, at three pre-specified timepoints (before surgery, end of surgery and postoperative day 1) will be calculated.
- Error grid analyses. The proportion of readings that fall in clinically acceptable regions A and B are presented, as per individual error grid calculations.
- %15/15 (equivalent to ISO 15197 2013) and %20/20 which is equivalent to the preceding version. %15/15 means that percentage of values that are within 15mg/dL of reference below 5.6mmol/L (100mg/dL) and within 15% above that threshold

Sensitivity analysis

For participants with/without diabetes mellitus, separate analyses will be undertaken.

5. Other analyses, data summaries and graphs

Clinical management

Clinical management for groups will be summarised but not subjected to statistical testing.

Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group:

- Use of insulin sliding scale
- Use of steroids intraoperatively.
- Use of vasopressor therapy.

6. References

1. Garg SK, Kipnes M, Castorino K, et al. Accuracy and Safety of Dexcom G7 Continuous Glucose Monitoring in Adults with Diabetes. *Diabetes Technol Ther* 20220221st ed. 2022; 24: 373–80
2. Chen JY, Nassereldine H, Cook SB, Thornblade LW, Dellinger EP, Flum DR. Paradoxical Association of Hyperglycemia and Surgical Complications Among Patients With and Without Diabetes. *JAMA Surg* [Internet] 20220615th ed. 2022; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/35704308>
3. Punthakee Z, Iglesias PP, Alonso-Coello P, et al. Association of preoperative glucose concentration with myocardial injury and death after non-cardiac surgery (GlucovISION): a prospective cohort study. *Lancet Diabetes Endocrinol* 2018/07/31 ed. 2018; **6**: 790–7
4. Welsh JB, Psavko S, Zhang X, Gao P, Balo AK. Comparisons of Fifth-, Sixth-, and Seventh-Generation Continuous Glucose Monitoring Systems. *J Diabetes Sci Technol* 20220613th ed. 2024; 18: 143–7
5. Klonoff DC, Freckmann G, Pleus S, et al. The Diabetes Technology Society Error Grid and Trend Accuracy Matrix for Glucose Monitors. *J Diabetes Sci Technol* SAGE Publications Inc; 2024; 18: 1346–61
6. Clarke WL. The original Clarke Error Grid Analysis (EGA). *Diabetes Technol Ther* 2005; **7**: 776–9
7. Freckmann G, Pleus S, Grady M, Setford S, Levy B. Measures of Accuracy for Continuous Glucose Monitoring and Blood Glucose Monitoring Devices. *J Diabetes Sci Technol* 2019; **13**: 575–83

Dummy tables

Table 1: Baseline Characteristics

	Non-diabetic	Diabetes Mellitus
Gender - no. (%)		
Male		
Female		
Age (years)		
Median (IQR)		
Current Smoker - no. (%)		
American Society of Anaesthesiology grade - no. (%)		
≥III		
Chronic comorbid disease - no. (%)		
COPD		
Asthma		
Interstitial lung disease or pulmonary disease		
Ischaemic heart disease		
Heart failure		
Liver cirrhosis		
Active cancer		
Stroke or transient ischaemic attack (TIA)		
Peripheral vascular disease		
Hypertension		
Planned surgical procedure - no. (%)		
Surgery involving the gut		
All other surgery		
Diabetes mellitus therapy		
- insulin		
- metformin		
- SGLT2i		
- glitazones		
- sulphonylureas		
Surgical procedure performed - no. (%)		
Surgery involving the gut		
All other surgery		
Cardiovascular medication - no. (%)		
Beta-blocker		
Calcium channel antagonist		
Doxazosin		
Diuretic		
Statin		
Nitrate		
Anti-platelet agents		
ACE-I/ARB		

Abbreviations: SD, standard deviation; IQR, Interquartile range; COPD, chronic obstructive pulmonary disease.

Table 2: Secondary outcomes

	Before surgery		End of surgery		24h after surgery	
	<i>Non-diabetic</i>	<i>DM</i>	<i>Non-diabetic</i>	<i>DM</i>	<i>Non-diabetic</i>	<i>DM</i>
Secondary outcomes						
Bias						
Secondary outcomes						
% MARD						
Risk zones (A, B, C, D, E)						

Table 3: Adverse events

Adverse events (n, %)	Non-diabetic	Diabetes Mellitus
Patients with ≥ 1 adverse event		
Type of adverse event		
Sensor failure		
Sensor alarm		
Removal- unplanned		
Other		

Dummy figures

Figures 1-4. Bland-Altman analysis & Diabetes Technology Error Grid – for each pre-specified timepoint plus all glucose measurements.