

# Randomised trial of Volatile vs Total intravenous Anaesthetic for major non-cardiac surgery

## Statistical Analysis Plan

Version 1.0  
Date: 24/11/2025

| Person(s) contributing to the analysis plan |                                                                                     |
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## 1. Administrative information

### Trial Information

|                                 |                                                                                    |
|---------------------------------|------------------------------------------------------------------------------------|
| <b>REC number:</b>              | 23/PR/0677                                                                         |
| <b>IRAS Number</b>              | 324653                                                                             |
| <b>Trial Sponsor:</b>           | Queen Mary University of London                                                    |
| <b>Trial Sponsor reference:</b> | 157967                                                                             |
| <b>Trial Funder:</b>            | Efficacy and Mechanism Evaluation, National Institute for Health and Care Research |
| <b>ISRCTN number:</b>           | ISRCTN46862025                                                                     |
| <b>Protocol version (date):</b> | 6.0                                                                                |

### SAP revision history

| Protocol version | Updated SAP version no. | Section number changed | List of changes from previous version/protocol | Author of change | Date |
|------------------|-------------------------|------------------------|------------------------------------------------|------------------|------|
|                  |                         |                        |                                                |                  |      |
|                  |                         |                        |                                                |                  |      |

### Members of the writing committee

Akshaykumar Patel (AP) wrote the statistical analysis plan, with input from Gareth Ackland (GA).

### Remit of the SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the GlucoVITAL trial. 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.

Secondary mechanistic studies exploring the relationship between glucose variability/absolute levels and: 1. Myocardial injury, 2. Infections, 3. Vasopressor use 4. Acute kidney injury will be covered in separate SAPs.

## 2. Background and trial design

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Full Title                   | Randomised trial of Volatile vs Total intravenous Anaesthetic for major non-cardiac surgery and its impact on glucose control                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Short Title                  | GlucoVITAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Study objectives             | <p>Primary:<br/>To determine whether TIVA reduces stress hyperglycaemia and perioperative glucose variability in the first 24h, compared to inhalational anaesthesia.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> <li>To compare interstitial glucose levels and variability between TIVA and inhalational anaesthesia groups in the first 24h</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Trial Design and Methodology | Single blind randomized trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Phase of the Trial           | Phase IIa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Study Setting                | Hospitals undertaking elective or urgent non-cardiac surgery in participating countries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Number of Patients           | 450 patients (225 patients per treatment arm)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| PICOT Summary                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Population                   | <p>Patients aged 50 years and over undergoing elective major noncardiac surgery under general anaesthesia.</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>Aged <math>\geq 50</math> years</li> <li>Elective major noncardiac surgery under general anaesthesia (as per PQIP inclusion criteria)</li> <li>Written informed consent for trial participation</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>Known contraindication to either TIVA or inhalational anaesthesia</li> <li>Clinical refusal</li> <li>Procedures where the participant is not expected to survive for 30 days</li> <li>Previous participating and completion in the GlucoVITAL trial</li> <li>Patient unable to give informed consent or complete questionnaires</li> </ul> |
| Intervention                 | Maintenance of anaesthesia by total intravenous anaesthesia (propofol)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Comparator Intervention      | Maintenance of anaesthesia by inhalational anaesthesia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Primary Outcome Measure      | Difference in blood glucose at the start and the end of surgery.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Secondary outcomes           | Continuous glucose measurements using CGM during first 24h from induction of anaesthesia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Maximum Treatment Duration   | Intraoperative period                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Follow-Up Duration           | 30 days from the day of surgery                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| End of Trial Definition      | When the last patient has completed their 30-day follow-up                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

### **3. Outcome measures**

#### **Primary Outcome:**

The primary outcome is the difference in absolute blood glucose (mmol/l) at the start and the end of surgery.

#### **Secondary Outcomes:**

1. Perioperative glucose variability: quantified using continuous glucose monitoring values (continuous data) over the first 24 hours postoperatively.
2. Days alive and home within 30 days of surgery: DAH30 is a continuous number between 0 and 30, reflecting the total number of days that a patient spends alive and at home within 30 days after surgery. In this definition, home reflects any place other than hospital. If a patient dies within those 30 days, their value is set to 0. DAH30 captures the development of all-cause complications which prevents patients leaving hospital after surgery.

### **4. Sample size and randomisation**

#### **Sample size calculation**

The primary outcome is change in intraoperative blood glucose. From previous VITAL data, mean blood glucose in 47 non-diabetic patients increased by 2.2mmol/L (SD:1.8) at the end of surgery. Assuming 5% 2-sided significance and 90% power, with a SD of glucose change by the end of surgery of up to 1.8mmol/L, at least 390 patients are required to detect a difference of 0.6mmol/L in glucose increases between modes of anaesthesia (allowing for nominal 2% dropout).

For secondary mechanistic studies, ~47% OPTIMISE/VISION-UK participants >50y sustain myocardial injury within the first 24 hours after surgery (~48%) and/or all-cause infection at any time before hospital discharge (~20% participants).<sup>18, 19</sup> With 450 patients recruited, we will have a 90% chance of detecting (at 5% 2-sided significance), a decrease in this composite outcome from 56% with inhalational versus 40% with intravenous anaesthesia (allowing for a 4% drop out).

#### **Randomisation**

Randomisation will occur on the day of the surgery but before the surgery is due to start. Before randomisation, the participant must have provided informed consent and it must be confirmed with the lead anaesthetist and/or surgeon on the day of the surgery that the procedure will go ahead. Participants are randomised on a 1:1 ratio to receive either TIVA or inhalational anaesthesia by a computer generated procedure. This computerised procedure will use a minimisation algorithm to ensure balance in treatment arm allocation across the following four stratification variables, factors thought to affect outcome either through treatment effectiveness or underlying prognosis, as originally defined by the initial parent trial VITAL:

1. Surgical speciality (musculoskeletal/intra-abdominal/thoracic/vascular/other)
2. Expected duration of surgery (<2hours, ≥2hours)
3. Cancer surgery/non-cancer surgery
4. Preoperative frailty (Rockwood Frailty Score) - Well/Vulnerable/Frail<sup>25</sup>

Each participant will be allocated to the treatment group that minimises between group differences in these factors among all participants recruited to the trial to date. The allocation sequence is generated by an automated algorithm and is concealed to all trial investigators. The system for generating the allocation sequence will be bespoke and will be developed in-house. The system will be validated for use by the trial statistician.

Recruiting centres will be asked to randomise participants on the day of surgery, once the planned surgery is confirmed as taking place. There will be occasions when surgery is cancelled at the last minute and rescheduled to another day. If the participant is happy to remain in the trial, recruiting centres will be asked to inform the GlucoVITAL team of the new surgery date as soon as possible, and data collection timepoints will be adjusted. Participants should receive their original allocated intervention at their new scheduled surgery date. If the surgery is cancelled indefinitely, or the participant is no longer suitable for the trial, the recruiting centre will be asked to inform the GlucoVITAL team as soon as possible.

## 5. Analysis methods

### General analysis principles

Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis and analysed according to the treatment to which they were randomised [1, 2]. Patients will be included in the analysis, regardless of whether the treatment they received was compliant with the protocol. Patients with missing outcome data will be excluded from the analysis. Missing data for baseline covariates to be included in the analysis model will be accounted for using mean imputation for continuous variables and the missing indicator approach will be used for missing data for categorical variables [3, 4].

For the analysis of the primary and secondary outcomes (excluding those not subjected to statistical testing) we will present the following information:

- The number of patients included in each analysis, by treatment group
- A summary statistic of the outcome (e.g. mean (SD), number (%)), by treatment group
- The estimated treatment effect
- 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.

### **Representativeness of patients**

All participating sites have been asked to keep a log of eligible patients not recruited to the trial. Reasons for non-participation will be categorised and summarised. Participation in the trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram [5].

### **Baseline characteristics**

Baseline characteristics will be summarised for each treatment group 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:

- Demographic: age (years), gender (male/female)
- ASA grade (I/II/III/IV)
- Frailty: Well to fit, Vulnerable, Frail
- BMI: Obese (BMI>30), Normal (BMI 18.5-25), Overweight (BMI 25-30), Underweight (BMI< 18.5)
- Medication for diabetes mellitus: Insulin (any duration of action), Metformin, DPP-4 inhibitors, GLP-1 receptor agonist, SGLT 2 inhibitor, Sulfonylureas, Thiazolidinediones, No medication for diabetes
- Other medication: None of the listed, ACE inhibitors, ARBs, Beta-blockers, Calcium channel blockers, Diuretics, Alpha-blockers, Nitrates, Statin, Antidepressants, Alpha-2 Agonists, Opioids, Benzodiazepines, Antiplatelet/Anticoagulant, Steroids, Immunosuppressants, Other
- Blood Results: Neutrophil count  $\times 10^9/L$ , Lymphocyte count  $\times 10^9/L$ , Estimated GFR (ml/min)
- Type of surgery: Hepatobiliary, Upper GI, Colorectal, Gynae/gynae-onc, Thoracic, Orthopaedic, Neuro, ENT, Vascular, Plastics, Other
- Indication of surgery: Active cancer, Other

### **Analysis software**

All analyses will be conducted in Stata Version 19 (StataCorp. 2025. *Stata Statistical Software: Release 19*. College Station, TX: StataCorp LLC.).

### **Analysis of primary outcome**

#### Primary analysis

The primary outcome, change in blood glucose (mmol/l) at the start and the end of surgery, will be analysed using a linear mixed-effects model on end-of-surgery glucose with random intercept for center. The model will be adjusted for minimisation variables as fixed factors which are surgical speciality (musculoskeletal/ intra-abdominal/ thoracic/ vascular/ other), expected duration of surgery (< 2hours,  $\geq 2$  hours), cancer surgery (yes, no) and preoperative frailty (well, vulnerable, frail) [6]. The model will also be adjusted for baseline start-of-surgery glucose, age and gender [7-9]. Baseline adjustment is recommended for randomized trials because it improves precision and controls for regression to the mean while preserving the randomized comparison [10]. We will estimate fixed effects with

restricted maximum likelihood (REML) and use small-sample degrees of freedom adjustments for fixed effects [11-12].

When participants are randomised according to incorrect baseline information, under the ITT principle they should be analysed in their allocated treatment group, irrespective of the fact that their allocation was based on incorrect information. The incorrect baseline information should be kept in the randomisation record, as this reflects how the randomisation was performed, and the correct information documented for use in an adjusted analysis [13].

### Missing Data

For the primary analysis, missing outcome data will be handled under a pre-specified Missing at Random strategy. If the proportion of participants missing end-of-surgery glucose is small ( $\leq 5\%$ ) and missingness is plausibly independent of the outcome conditional on observed covariates, the analysis will proceed as complete case. Otherwise we will use multiple imputation by chained equations (MICE) assuming MAR, with end-of-surgery glucose imputed from treatment group, baseline (start) glucose, all minimization factors (surgical specialty, expected duration of surgery, cancer surgery and frailty), center (included as a categorical predictor), and prespecified auxiliary variables that are predictive of missingness and/or outcome. At least 40-50 imputations will be generated, with diagnostics (convergence checks, distributions vs. observed, and plausibility bounds) documented. The ANCOVA will be fitted within each imputed dataset and combined using Rubin's rules to report the adjusted treatment effect, 95% confidence interval, and p-value [14-15]. Missingness rates and patterns will be summarized by randomized group and center.

### Sensitivity analyses

1. Regardless of the missing data, will perform a sensitivity linear mixed effects model, estimation will use restricted maximum likelihood and include all start and end measurements. Under the MAR assumption given observed covariates (treatment group, time, minimization factors and center), maximum likelihood provides unbiased and efficient estimates without explicit imputation; participants with one missing timepoint (start or end) remain in the analysis, while those missing both contribute no information and are excluded. Degrees of freedom for fixed effects will use Kenward-Roger or Satterthwaite approximations as supported. This provides a methodologically distinct but Estimand aligned check for the primary analysis. We will compare the treatment effect from this model (group x time interaction) to the primary estimate. If notable discrepancies arise, we will review missingness mechanisms and conduct targeted sensitivity checks to assess the robustness of conclusions to departures from MNAR.
2. If the primary ANCOVA analysis (with MAR handling as above) and the sensitivity mixed-effects model disagree beyond chance after alignment of covariates and coding, a tipping point analysis will be conducted to assess robustness to

departures from MAR (i.e., missing not at random, MNAR). Starting from the MAR multiple imputation, we will add deltas to imputed end of surgery glucose values for participants with missing outcomes, then re-estimate the primary model across a grid of delta values spanning clinically plausible deviations (eg, -1.0 to 1.0 mmol/L in 0.25 mmol/L steps), considering both equal and differential shifts by group. We will report the adjusted treatment effect and 95% CI at each delta and identify the smallest delta that changes the primary outcome conclusion. This delta-adjusted pattern-mixture approach preserves imputation uncertainty with the analysis model, and is recommended MNAR sensitivity approach in clinical-trial practice [16-18]

### Analysis of secondary outcomes

#### Glucose variability, quantified using continuous glucose monitoring values over the first 24 hours postoperatively

We will analyse the entire CGM glucose time series with a linear mixed-effects model using flexible time terms and a group-by-time interaction, random intercepts for center and participant. The time scale will be defined as a 0 to 24 hour window with readings taken every 5 mins after the end of surgery. Fixed effects will include treatment group, surgical specialty, duration of surgery, cancer surgery and preoperative frailty. To capture the nonlinear evolution of glucose over time, we will represent time with a restricted cubic spline over hours 0 to 24, with knots at clinically sensible positions such as 0, 6, 12, 18 and 24 hours, and we will include interactions between group and each spline basis function so that trajectories can differ by treatment across the entire window [19]. To account for clustering and within-person correlation, we will include a random intercept for center and both a random intercept and a random linear time slope for each participant. The model for glucose  $G$  at time  $t$  for participant  $i$  in center  $c$  is specified as:

$$G_{it} = y_0 + y_1 \times trt_i + \sum_{m=1}^M y_{2m} \times s_m(t) + \sum_{m=1}^M y_3 \times (trt_i \times s_m(t)) + y_4 \times Z_i + u_{c(i)} + b_{0i} + b_{1i} \times t + \varepsilon_{it},$$

where  $s_m(t)$  denotes the spline basis functions of time,  $Z_i$  denotes the prespecified covariates,  $u_{c(i)}$  is the center-level random intercept, and  $b_{0i}, b_{1i}$  are the participant-level random intercept and linear time slope.

Our primary inferential test will assess whether the postoperative glucose trajectories differ between treatment groups over the full 24-hour period by testing the joint null hypothesis that all group-by-time interaction coefficients equal zero. From the same model, we will present and plot adjusted marginal mean glucose trajectories by treatment group over 0 to 24 hours, the average 24-hour difference between groups computed as the time-mean of the adjusted group difference and adjusted differences at prespecified time points such as 1, 6, 12, 18 and 24 hours.

We will also report descriptive statistics including blood glucose measured at each pre-specified timepoint (before surgery, end of surgery, morning after surgery), the Coefficient of Variation, Mean Absolute Glucose (MAG), Continuous Overall Net Glycaemic Action

(CONGA),<sup>1</sup> % time above 10mmol/l and below 3.8mmol/l within 24 hours of CGM sensor placement.

### DAH30

Number of days spent in hospital in case of readmission within 30 days of surgery will not be subjected to statistical testing and will be summarized using mean (SD) and medium (IQR, alongside a bar chart by treatment group.

### **Strategy for analysis of primary and secondary outcomes if model fails to converge**

If the statistical models for any of the primary or secondary outcomes do not converge, then the following steps will be taken:

1. The model will be fitted without a random intercept for trial centre
2. As above, but excluding any additional covariates apart from minimisation variables
3. As above but also excluding minimisation variables.

### **Plan in case of over-stratification**

When adjusting for covariates in the primary analysis or secondary analysis models where the outcome is binary, if there is a category within that covariate where no events have occurred in either of the treatment groups, the statistical model will exclude all patients within this category. To overcome this, this category will be merged with another category; this will be decided by the chief investigator who will be blinded to results. This will apply to covariates with three or more categories. However, if all but one category within that covariate have no events recorded in one of the treatment groups then we will exclude this covariate from the model.

### **Subgroup Analyses**

Subgroup analyses will be used to explore whether the effectiveness of the intervention differs for participants with different characteristics. The analysis of the primary and secondary outcome will be repeated introducing an interaction term between treatment allocation and the subgroup of interest into the model. The same analysis model will be used as for the primary and secondary analysis adjusting for the same covariates used in the analysis and the subgroup variable of interest. We will consider the following subgroups:

1. Complications (Clavien-Dindo  $\geq 2$ )

## 6. Other analyses, data summaries and graphs

### Complications within 30 days after surgery

The number and percentage of patients experiencing any complication with a Clavien-Dindo  $\geq 2$  will be presented by treatment group.

### Safety analyses

Serious adverse events will be presented as a number (%) by treatment group. All patients with a recorded outcome will be included in the summary. In addition to this, 'other' adverse events will be reported separately if prevalence is more than 5% across all participants in the trial.

### Protocol Deviations

Numbers and percentages of protocol deviations will be reported. The following protocol deviations will be reported: (a) non-adherence to randomized allocation; (b) failure to take blood samples at any stage of the three pre-specified timepoints (before surgery, end of surgery, morning after surgery). We will report the number of patients in each treatment group with at least one of the above protocol deviations. In addition to this, 'other' protocol deviations will be reported separately if prevalence is more than 5% in the trial.

### Clinical management

Clinical management for the TIVA group and inhalational anaesthesia group will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group. The TIVA and inhalational anaesthesia will be compared for the following clinical management characteristics:

- Type of analgesia: Opiates alone, Neuraxial +/- peripheral nerve block
- Arterial glucose
- Dexamethasone and/or steroids given
- Insulin infusion
- Systolic BP  $<90$ mmHg after induction of anaesthesia
- Vasopressor infusion during or after surgery
- Duration of surgery, minutes
- Intravenous fluids (ml)
- Packed red cells (ml)

### Postoperative day one of surgery

Postoperative day one of surgery characteristics for the TIVA group and inhalational anaesthesia group will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group. The following characteristics will be summarized:

- Arterial glucose
- Insulin infusion
- Neutrophil count day one after surgery  $\times 10^9/L$
- Lymphocyte count day after surgery  $\times 10^9/L$

- Systolic BP < 90mmHg
- Vasopressor support

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