Joint Research Management Office (JRMO) Research Protocol for Research Studies

Full Title	GlucoVITAL – Observational mechanistic sub-study of the Volatile vs Total intravenous Anaesthetic for major non-cardiac surgery (VITAL) trial
Short Title	GlucoVITAL
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IRAS Number	324653
Sponsor (EDGE) Number	157967
REC Reference	23/PR/0677
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Contents

1. Glossary

CI	Chief Investigator
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
HRA	Health Research Authority
IRAS	Integrated Research Application System
ISF	Investigator Site File
Participant	An individual who takes part in a clinical study
PI	Principal Investigator
QMUL	Queen Mary University of London
REC	Research Ethics Committee
TMF	Trial Master File

2. Signature Page

CI Agreement

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of GCP, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

CI name:	**Professor Gareth Ackland**
Signature:	Gareth Ackland Digitally signed by Gareth Ackland Date: 2023.08.16 10:26:57 +01'00'
Date:	**16-08-2023**

3. Summary and Synopsis

Short title	GlucoVITAL
Methodology	National, multi-centre prospective observational cohort study nested within the VITAL trial
Objectives	1. Measuring intraoperative glucose levels 2. Examine whether total intravenous anaesthesia (TIVA) reduces common complications (myocardial injury and/or infectious complications) by limiting hyperglycaemia after major noncardiac surgery 3. Detecting the individual's risk of developing injurious perioperative hyperglycaemia
Number of participants	450 participants
Eligibility criteria	Patients aged 50 years and over undergoing elective major noncardiac surgery under general anaesthesia and consented into the VITAL trial
Statistical methodology and analysis	For the primary outcome of intraoperative blood glucose
Study duration	24 months

4. Introduction

4.1. Background

The frequent development of high blood glucose levels (stress hyperglycaemia) early during major surgery[1] is consistently and dose-dependently associated with myocardial injury[2] and infections[3], both of which prolong hospitalisation and accelerate mortality even after discharge from hospital[4]. The majority of individuals who experience complications after surgery associated with hyperglycaemia do not have diabetes mellitus[5]. Hyperglycaemia, which occurs in part through the development of insulin resistance[1], exacerbates systemic inflammation through acute oxidative stress, leading to organ injury[6]. The risk of sustaining myocardial injury and infections doubles with hyperglycaemia, yet routine detection of injurious levels of hyperglycaemia is not a routine feature of current practice[5]. Moreover, anaesthetic techniques that limit stress hyperglycaemia are unexplored, despite substantial mechanistic differences between intravenous and inhalational anaesthetic agents that alter the risk of disrupting normal glucose control[1].

The surgical backlog presents a huge challenge to not only increase surgical throughput, but also ensure complications after noncardiac surgery are minimised[7]. At least 50% of individuals develop high blood glucose levels (hyperglycaemia) after tissue injury/trauma [8], which are associated with, and mechanistically linked to, organ injury and infections after surgery. Numerous mechanisms are likely to contribute to perioperative hyperglycaemia, characterized by a state of insulin resistance - a state of decreased biological response to insulin. Many individuals without diabetes mellitus have established insulin resistance before surgery, a key component of metabolic syndrome which is present in ~25% of the UK population[9]. Mitochondrial bioenergetics controls insulin sensitivity by regulating the cellular redox environment[10], with impaired mitochondrial electron transport and fatty acid oxidation evident in insulin resistance across diverse tissues[11]. Acquired mitochondrial and glycolytic dysfunction occurs in circulating lymphocytes after surgery, as quantified by ex- vivo respirometry[12], leading to impaired functionality[13] and cell death[12]. Acute loss of adaptive immune cells results in the failure to temper the inflammatory response generated by the initial innate response to tissue injury[14]. Reduced numbers of T-cells exacerbate systemic inflammation[14 15] and increases the risk of infection[16] and organ injury[17], including after surgery[18].

Despite these startling links and potentially treatable perioperative abnormalities, routine detection of perioperative hyperglycaemia is not a routine feature of current practice in individuals without diabetes mellitus**,** unless they are admitted to a high-dependency/critical care unit.

Paradoxically, poor outcomes have been repeatedly shown to occur in patients without diabetes who develop perioperative hyperglycaemia, compared with patients with diabetes mellitus.[5 20] Rational therapy is limited by the lack of easy-to deliver glucose monitoring at scale,[1] as well as ongoing controversy over limiting serious side effects of hypoglycaemia frequently associated with exogenous insulin therapy.[23 24] Postoperative hyperglycaemia may be the most important risk factor for surgical site infections.[25] A Cochrane analysis found insufficient evidence to support strict glycaemic control versus conventional management (maintenance of glucose <10mmol.L^{-1}) for the prevention of surgical site infections.[19] These data are limited by methodological quality, including small sample sizes in single-centre studies plus inconsistencies in glucose measurement and outcome measures. Perioperative hyperglycaemia is also associated with excess myocardial injury[2]. Sustaining subclinical myocardial injury is associated with higher risk of mortality one year after surgery[26].

Recently, another key study has reported outcomes in 4899 non-diabetic individuals in whom a very high prevalence of blood glucose testing (75%) occurred within 24 hours after surgery[5]. Hyperglycaemia was defined, a priori, as blood glucose level of ≥7.8mmol/L within 24 hours after surgery. This study confirmed that patients without diabetes mellitus had worse outcomes than patients with diabetes at similar levels of hyperglycaemia. The authors speculated insulin may mitigate this effect, but this has huge implications for service delivery, patient safety and would require a complete redesign of perioperative glucose monitoring to identify patients who may benefit from treating higher glucose levels. However, the challenges of insulin administration at scale, plus the frequent danger of hypoglycaemia as illustrated by the NICE-SUGAR trial in critically ill patients[23], suggests that alternative therapies to minimise blood glucose require exploration. Ideally, a real-time monitor to alert clinicians to injurious levels of hyperglycaemia in a non-critical care setting and/or a preoperative test to detect individuals most at risk would rationalise resources. That is now a reality – albeit untested- using continuous (interstitial) glucose monitoring.

4.2. Rationale

Our aims of the study are to provide detailed data describing the below questions:

1. Measuring intraoperative glucose levels
2. Examine whether total intravenous anaesthesia (TIVA) reduces postoperative complications (myocardial injury and/or infectious complications) by limiting hyperglycaemia after major noncardiac surgery.
3. Detecting the individual's risk of developing injurious perioperative hyperglycaemia

5. Study Objectives

5.1. Primary objective

To identify association between intraoperative glucose levels and the mode of anaesthesia (total intravenous anaesthesia vs inhalational) in patients undergoing major noncardiac surgery.

5.2. Secondary objectives

To determine whether:

(1) Days alive and at home at 30 days (DAH30)

(2) Total intravenous anaesthesia reduces myocardial injury and/ or postoperative infection by limiting hyperglycemia

(3) Establish the interaction between absolute glucose levels and mode of anaesthesia in the perioperative period

(4) Patients with, or susceptible to insulin resistance can be identified prior to surgery

5.3. Primary clinical outcome measure

The primary outcome is blood glucose measurements via:

1) Blood-Gas measurements for glucose before surgery, the end of surgery and on day one after surgery.
2) Continuous glucose measurements using continuous glucose monitoring (CGM) up to 10 days after surgery or hospital discharge whichever is sooner.

5.4. Secondary clinical outcome measures

1) 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.
2) Increase in serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) concentration of:
    a. An absolute value of ≥15ng L^{-1} on day one after surgery

    OR

    b. An increase of ≥5 ng L^{-1} from the preoperative value on day one after surgery when the preoperative value of ≥15ng L^{-1}
3) Incidence of postoperative infection within 30 days after surgery. This is defined as one or more of the following infections of Clavien-Dindo grade II or greater. A full list of definitions is available in Appendix 1:
    a. Superficial surgical site infection;
    b. Deep surgical site infection;
    c. Organ space surgical site infection;
    d. Pneumonia;
    e. Urinary tract infection;
    f. Laboratory confirmed blood stream infection;
    g. Infection, source uncertain; this is defined as an infection which could be more than one of the above (i.e. a-f), but it is unclear which.

5.5. Explanatory/ mechanistic outcome measures

1) Plasma C-peptide measurements before surgery, the end of surgery and on day one after surgery.
2) Insulin measurements before surgery, the end of surgery and day one after surgery.
3) Flow cytometry assessment of metabolic dependence of mononuclear cells before surgery, the end of surgery and day one after surgery.*

** This will only be done at Barts NHS Trust and Royal Marsden.*

5.6. Assessment of primary and secondary outcomes

The blood-gas measurements for glucose will be recorded on 1) the day of surgery before induction of anaesthesia, 2) the end of surgery defined as time at which surgical drapes are removed and 3) day after surgery (10:00am ± 6 hours). Real time continuous glucose monitoring will be measured using a Dexcom G7 sensor. The patient will wear these monitors continuously from induction of anaesthesia to up to 10 days postoperatively [maximum usage duration for each sensor] or hospital discharge whichever occurs sooner. The glucose monitor will be provided by the Sponsor.

Participants will be contacted by telephone at Day 30 (+ 2 days) by site research staff to collect data on hospital readmission and any postoperative complications that classed as Clavien-Dindo Severity Grade II or above (Appendix A and B).

Blood samples (approximately 15 ml) will be collected to measure:

1) *Myocardial injury*: Plasma high sensitivity troponin-T (Elecsys, Roche Diagnostics) levels will be measured in blood samples collected on the day of surgery before the induction of anaesthesia and on day one after surgery (10:00am ± 6 hours).

2) *Presence and/or development of insulin resistance*: Plasma C-peptide and insulin levels (ELISA assays) will be measured on the day of surgery before the induction of anaesthesia, within 2 hours after the end of surgery (defined as time at which surgical drapes are removed), and on day one after surgery (10:00am ± 6 hours).

3) *Leukocyte and metabolic profiles:* Whole blood will be analysed by flow cytometry on the day of surgery before the induction of anaesthesia, within 2 hours after the end of surgery (defined as time at which surgical drapes are removed), and on day one after surgery (10:00am ± 6 hours).

When assessing the Clavien-Dindo complications, if the initial assessment will be made by a research associate; this will typically be a research nurse, but may include physicians and surgeons. This initial assessment by the research associate will be based on clinical information including information from patients' medical notes, including (but not limited to) microbiology test results, blood test results, drug prescription charts, radiology tests etc. Patients discharged from hospital before day 30 will be contacted shortly after day 30 to ascertain whether they have received any new treatment since discharge, or if they have been re-admitted to hospital or seen a

doctor since discharge. For patients who have received further treatment or seen a health professional since discharge, further details will be collected directly from the hospital/doctor or from the patient's health records to be used in the research associate's assessment. If the initial assessment by the research associate is of 'no infection', then the patient's outcome is classified as 'no infection'. If the initial assessment is of 'infection', then this decision must be confirmed by the site Principal Investigator (PI), who will evaluate the information used by the research associate in their initial assessment. The PI's decision is final; they can either confirm the research associate's initial assessment of 'infection' (in which case the patient's outcome is classified as 'infection'), or they can refute it (in which case the patient's outcome is classified as 'no infection').

6. Study Design

6.1. Study setting

National, multi-centre prospective observational cohort study nested within the VITAL trial. The list of all participating sites can be found at the beginning of the protocol.

6.2. Inclusion criteria

- Patients aged 50 years and over undergoing elective major noncardiac surgery under general anaesthesia and consented to the VITAL trial.
- Written informed consent for study participation

6.3. Exclusion criteria

- Known contraindication to either total intravenous anaesthesia or inhalational anaesthesia.
- Clinical refusal
- Procedures where the participant is not expected to survive for 30 days
- Previous participation and completion in the VITAL trial
- Patients unable to give informed consent or complete questionnaires

6.4. Recruitment and informed consent

Potential participants will be screened by research staff as part of the VITAL trial. Following consent into the main VITAL trial, participants will be approached to take

part in GlucoVITAL. This may be conducted via telephone, online or face-to-face consultations and provides an opportunity for the research team to explain the study to the participants in detail. Patient information sheets can be posted or emailed to participants for their perusal and consideration. The participant will be approached prior to surgery at the first suitable opportunity to allow time for any questions. It is recommended (although not mandated) that the participant is approached at least one day prior to the date of surgery. Written informed consent must be obtained before surgery. It is the responsibility of the Principal Investigator at each site, or persons delegated by the Principal Investigator to obtain written informed consent from each potential participant prior to participation in this trial. This process will include provision of a patient information sheet accompanied by the relevant consent form, and an explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The Principal Investigator or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and consent form will be reviewed and updated if necessary. The Principal Investigator or designee will assess potential participant's capacity to give informed consent, and those who lack capacity to give or withhold informed consent will not be recruited. If a participant loses capacity during their participation in the trial, the original consent by the participant will be respected. If this situation occurs, clinical outcome data will continue to be collected, but participant questionnaires will not need to be completed. Patients who are not entered into this trial should be recorded (including reason not entered) on the electronic patient-screening log provided to sites.

6.5. Informed consent considerations

The right of a participant to refuse participation without giving reasons will be respected. The participant remains free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, for example if during the trial new research safety information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a participant, the PI will ensure this is done in a timely manner.

Visit	1	2	3	4	5	6
Visit Window	**Day 0 pre-op**	**Day 0 post-op**	**Day 1[#] post-op**	**Day 2-Day10 post-op**	**Day of discharge[#]**	**Day 30 + 2 days**
Informed consent	x					
Medical history	x^					
Inclusion/exclusion criteria	x					
Surgical speciality	x^					
Expected duration of surgery (<2hrs, ≥2hrs)	x^					
Cancer surgery/non-cancer surgery	x^					
Preoperative frailty (Rockwood Frailty Score)	x^					
Collection of trial blood sample	x[$]	x[$]	x[$]			
Blood gas glucose measurement	x[$]	x[$]	x[$]			
Real time continuous glucose monitoring	x[$]	x[$]	x[$]	x[$]		
Bauer questionnaire			x^			
QoR-15				x^		
Brice questionnaire				x		x
Post-operative delirium (4AT)				x		
Post-operative complications (Clavien-Dindo Grade II and above)						x^
Length of stay*					x^	
Survival status*						x^
Hospital readmission*						x
Quality of Life EQ 5D	x^				x^	x^

*Information needed for DAH30
^ Already collected as part of the main VITAL trial
[$] and highlighted in red are data collected only as part of GlucoVITAL
[#] Or closest next working day

6.6. Written/ reading / translation considerations

The research team will not recruit participants unless the patient information sheet, consent form and video are provided in the appropriate language.

6.7. Schedule of assessment

Data will be collected on all eligible patients during the study recruitment period after informed consent.

6.8. End of trial definition

The end of the trial (EOT) is defined as 180 days from the when the last patient had completed their 30 day follow-up.

7. Laboratories and samples

7.1. Central laboratories

Myocardial injury will be assessed based on serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) and the analysis will be conducted by The Doctor's Laboratory.

7.2. Local laboratories

C-peptide analysis and insulin resistance will be measured on plasma samples (ELISA, ABCAM) and the analysis will be conducted by the Chief Investigator in the Translational Medicine and Therapeutics laboratory, William Harvey Research Institute (WHRI).

7.3. Sample collection and labelling logging

All blood samples will be pseudo-anonymised. Samples collected at each participating site will be labelled with the participant's corresponding study ID and kept in a hospital freezer at an optimal temperature for the troponin assay until collection. The samples will be routinely collected and transferred to WHRI where they will be stored prior to transfer to The Doctor's Laboratory for analysis. The full sample, collection, labelling, logging and transfer procedure will be documented in the study laboratory log.

7.4. Sample receipt/chain of custody/accountability

Handling of the samples upon arrival at the local and central laboratory will be documented. All samples will be logged upon receipt and the laboratory will ensure that the physical integrity of these samples have not been compromised in transit. If

compromise has occurred, the trial coordinating team, as well as the Sponsor, will be informed of this. Upon receipt of samples, laboratory staff will ensure that all samples are accounted for as per the labelling.

7.5. Sample storage procedures

The samples should be put in the freezer within two hours of preparation. The samples will not be destroyed if a patient withdraws from the study unless they specifically request so. If the patient requests for the samples to be destroyed the Tissue Custodian (CI), will inform the lab who will ensure the samples are destructed as per the Human Tissue Act. This will be documented in the Trial Master File and Investigator Site File of the participating site.

7.6. Sample and data recording/reporting

Troponin-T data will be measured by the central laboratory and shared by secure electronic communication after the last patient sample has been analysed.

7.7. End of study

The samples will be stored beyond the end of the trial to be used for closely related studies in the future. After completion of any potential sub-studies the samples will be destroyed according to the Human Tissue Authority's Code of Practice.

8. Statistical considerations

Statistical analyses will be conducted by parent VITAL CTU statisticians, conducted once the main VITAL data are analysed. A detailed statistical analysis plan will be drafted by the trial statistician, which will be finalised and approved by the Chief Investigator and an independent statistician before the final data analysis. All statistical analyses will be undertaken on an intention to treat basis to preserve randomisation, avoid bias from exclusions and preserve statistical power. Hence all participants enrolled into the study, regardless of whether they received their randomised intervention, will be analysed according to their randomised group using data collected up to their 30-day time-point, or the last time-point prior to their withdrawal or loss to follow-up before this. Patients not receiving surgery or withdrawing consent for follow-up prior to surgery will not be included in relevant denominators.

For the primary outcome of blood glucose change from the start of surgery until the end of surgery, each randomised treatment arm's point estimates (and 95% confidence interval) will be reported. In addition, blood glucose measurements from the start of surgery until the end of surgery will be compared across randomised treatment arms using independent samples t-tests, or Wilcoxon rank sum tests depending on the distribution of the data. The secondary clinical outcomes (incidence of myocardial injury and/or all-cause infection) will be assessed across trial arms using a chi-squared test. The continuous variables measuring mechanistic outcomes of glucose and metabolic profiles will initially be compared across trial arms using independent samples t-tests, or Wilcoxon rank sum tests (depending on the distribution of the data). Further comparisons across trial arms of blood glucose measures over time and the mechanistic outcomes over time will use repeated measures analyses, a statistically efficient approach that allows all of the follow-up data collated during the study to be used.

For GlucoVITAL, four factors define sub-groups of interest: (1) Surgical speciality (intrabdominal/other); (2) cancer surgery/non-cancer surgery; (3) incidence of hyperglycaemia (glucose <7.8mmol/L) within first 24h of surgery (including at time of induction of anaesthesia); (4) diabetes mellitus/no diabetes mellitus. Pre-specified sub-group analyses that will be undertaken using appropriate modelling techniques. These will be determined following examination of the distributions of the collected data. These exploratory sub-group analyses will have lower power than the main whole trial analysis but are hypothesis-generating and results will be scrutinised graphically via forest plots.

Descriptive statistics will be used to summarise the distribution of baseline variables across each of the randomisation arms. Continuous variables will be reported with means and 95% confidence intervals, if normally distributed, or medians and Interquartile Ranges (IQR) otherwise. Categorical variables will be reported using frequencies and percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of participants:

- Assessed for eligibility
- Excluded prior to randomisation (and the frequency of each reason for exclusion)

- Allocated to each randomisation arm
- Receiving or not receiving their randomised treatment
- Followed-up at each protocol specified timepoints
- Lost to follow-up at each protocol specified timepoints (plus frequency of each reason for loss to follow-up)

8.1. Sample size

The primary outcome intraoperative blood glucose. From current 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 the secondary (composite) clinical outcome: ~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). 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). We will also record DAH30, which reflects composite complications after surgery.

Mechanistic outcomes*:* glucose and metabolic profiles after surgery in each anaesthetic group will be quantified by:

(a) Continuous glucose monitoring: *c*omplications are twice as likely when blood glucose is >7.8mmol/L within 24 hours after surgery, which occurs in ~50% individuals without previous diabetes [5]. We will therefore examine the interaction between blood glucose levels in the range of 3.9-7.8mmol/L within 24 hours of surgery and anaesthetic type with secondary outcomes. (1) glycaemic area under the curve; (2) time in range will be defined as % total time within glucose range 3.9-7.8mmol/L within 24 hours of surgery, and for the duration of sensor measurements (maximum 10 days, or hospital stay <10 days).

(b) Insulin resistance: The Homeostatic Model Assessment for Insulin Resistance (HOMAIR) will be used to estimate insulin resistance. Paired fasting plasma glucose and C-peptide will be quantified by lab personnel blinded to clinical/glucose data. Based on previous work examining the effect of methylprednisolone on insulin resistance [44], 45 patients per arm are required to have a 90% chance of detecting (5% 2-sided significance) a difference of 1 SD (0.6) in HOMA-IR between intravenous and inhalational anaesthesia 24 hours after surgery (2% dropout).

(c) Flow cytometry quantification of glutamine dependence of T cells will be undertaken before induction of anaesthesia and 24 hours after surgery. Assuming 5% 2-sided significance, SD of glutamine dependence of up to 7% and 90% power, 133 patients are required to detect a difference of 4% in glutamine dependence between modes of anaesthesia (allowing for nominal 2% dropout).

9. Ethics

The Chief Investigators must ensure that the study is conducted in accordance with the guidelines of the International Conference on Harmonisation, Good Clinical Practice (GCP) and UK legislation. All study documentation will be reviewed and approved by the research ethics committee prior to start of recruitment. Research Ethics Committee, Health Research Authority and Sponsor approvals will be in place before patient recruitment commences. The study will be sponsored by QMUL. Additionally, each participating site will ensure that the approval of the relevant trust Research & Development department and Ethics Committee is in place and a written confirmation is provided to the Sponsor.

9.1. Annual Safety Reporting

This is an observational study and there is no risk of harm to either patients or investigators. The Dexcom G7 Continuous Glucose Monitoring System (Dexcom G7 CGM System or G7) is a glucose monitoring system indicated for continuously measuring glucose in the interstitial fluid in persons age 2 years and older, including pregnant women, under CE mark in Europe.

10. Public Involvement

The grant proposal for this study has been designed with the PPI members at The Patient, Carer & Public Involvement and Engagement (PCPIE) group (support (https://www.niaa-hsrc.org.uk/PCPIE). Furthermore, our PPI co-applicant have reviewed the protocol and will continue to advise us for the duration of the study including dissemination of the study results. Patient research partners will review the protocol and patient-facing documents to ensure that they are fit for purpose and refine our consenting procedures. They will join our regular Trial Management Committee meetings and review participant recruitment progress.

11. Data Handling and Record Keeping

11.1. Information governance

The study will be sponsored by Queen Mary University of London and will follow NHS and sponsor standard operating procedures for data storage and access and are consistent with the principles of the Data Protection Act and General Data Protection Regulation (GDPR).

11.2. Data management

Data will be transcribed onto the electronic CRF (eCRF) on the secure data entry web portal. Submitted data will be reviewed for completeness and consistency by authorised users within the trial coordinating team. Submitted data will be stored in Queen Mary University of London safe haven securely against unauthorised manipulation and accidental loss. Only authorised users at site, or at Barts Health NHS Trust will have access. Desktop security is maintained through usernames and passwords. Data back-up procedures are in place and a full audit trail will be kept. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK).

The data analysis for GlucoVITAL will be run in collaboration with the University of Warwick. As a result, GlucoVITAL will be utilising the VITAL data collection platform with the addition of some added data collection fields in order to complete the outcome analysis. The data collection processes and processing activities will be detailed in the collaboration agreement between both parties.

11.3. Source Data

The eCRF will count as source data for patient reported outcomes collected during the 30-day follow-up. Patients' medical notes will act as source for the rest of the data. It is expected that the exact source data list will vary by site.

11.4. Confidentiality

The Principal Investigator has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. The Chief Investigator and the study team will adhere to these parameters to ensure that the participant's identity is protected at every stage of their participation within the study. Patients will be anonymised with regards to any publications relating to this study.

11.5. Record retention and archiving

During the course of research, the Chief Investigator has full responsibility of all study records which must be kept in secure conditions at all times. The UK Policy Framework for Health and Social Care Research and sponsor SOP, requires that research records are kept for five years after the study has completed. Archiving will be authorised by the Sponsor following submission of the end of study report. The Sponsor is responsible for maintaining and archiving the study TMF. The study database will be stored according to the Sponsor's policies. Electronic data sets will be stored indefinitely. The sites are responsible for maintaining and archiving all local records including the ISF and CRFs. These records should be archived together once authorisation has been given by the Sponsor. It is the responsibility of the Principal Investigator to ensure a full set of records is collated and documented.

12. Monitoring and Auditing

The sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable. The GlucoVITAL study master documents may be audited by the sponsor to ensure study activities are conducted according to the protocol, the sponsor's standard operating procedures, GCP and the applicable regulatory requirements. In participating hospitals, local study documents may be selected for audit on a local basis. However, the GlucoVITAL study team will not routinely monitor data collection in individual hospitals or conduct source data verification.

13. Study Management

The GlucoVITAL study will be managed by the Critical Care and Perioperative Medicine Research Group (CCPMG) based at Queen Mary University of London. The day-to-day conduct of the study trial will be led by the trial management group, under the management of the Chief Investigator(s) or nominated deputy.

14. Finance and Funding

The GlucoVITAL study is funded by the Efficacy and Mechanism Evaluation (EME) Programme awarded to the Chief Investigator. The funders will play no role in study design, conduct, data collection, data analysis, reporting or interpretation of the results.

15. Sponsorship and Insurance

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

16. Dissemination of Research Findings

Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the GlucoVITAL study group. At least one of the lay members will contribute to the dissemination of protocol and final manuscripts. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the design, committee membership, accrual of

eligible patients and statistical analysis. All authors will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. The funders, contributing centres (and participating investigators) will be acknowledged in the final manuscript. No investigator may present data from his/her centre separately from the rest of the study results unless approved by the study management team and the sponsor. The full study report will be submitted to the funder and will also be made accessible via ISRCTN.

17. References

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