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

Full Title	Perioperative complications and autonomic dysfunction assessed by the COMPASS-31 assessment tool
Short Title	periCOMPASS-31
Sponsor	Queen Mary University of London (Queen Mary) Contact person: Dr Mays Jawad Research Governance Operations Manager Joint Research Management Office Dept W, Research Services 69-89 Mile End Road, London, E14 UJ Phone: 020 7882 7275/6574 Email: research.governance@qmul.ac.uk
IRAS Number ***Integrated Research Application System***	328971
Sponsor (EDGE) Number	
REC Reference ***Research Ethics Committee***	
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List of laboratories	William Harvey Research Institute John Vane Science Centre Charterhouse Square, London, EC1M 6BQ

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1. Glossary

ASA	American Society of Anesthesiologists
CCPMG	Critical Care and Perioperative Medicine Research Group
COMPASS-31	Composite Autonomic Symptom Score-31
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PCPIE	The Patient, Carer & Public Involvement and Engagement
StEP-COMPAC	Standardised Endpoints and Core Outcome Measures for Perioperative Medicine and Anaesthetic Care
WHRI	William Harvey Research Institute

2. Signature page

CI Agreement

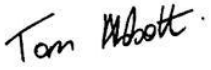
The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of GCP, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and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

CI Name:	**Professor Gareth Ackland**
Signature:	
Date:	**08-07-2025**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research,, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for the statistical work in this protocol is accurate and take responsibility for statistical analysis and oversight in this study.

Statistician's name:	**Dr Tom Abbott**
Signature:	
Date:	**08-07-2025**

3. Summary and synopsis

Short title	peri-Compass-31
Methodology	Observational study
Objectives	To provide a mechanistic understanding of why, and which elements of, autonomic dysfunction predisposes individuals to infectious and/or cardiovascular complications following major noncardiac surgery.
Number of participants	296
Inclusion and exclusion criteria	Inclusion criteria • Patients aged ≥ 50 years and over undergoing elective major noncardiac surgery under general anaesthesia expected to require at least an overnight stay in hospital. Exclusion criteria • Inability or refusal to provide written informed consent. • Inability to complete questionnaires. • American Society of Anesthesiologists (ASA) score of I.
Study duration	24 months

4. Introduction

4.1. Background

Experimental and clinical association studies show that autonomic dysfunction causes, or augments, systemic inflammation,[1] infections,[2] myocardial injury,[3] gastrointestinal complications[2] and lung injury.[4] As perioperative morbidity typically involves several organs, generalised loss of autonomic function is a plausible unifying pathological driver underlying infectious complications after major surgery. However, screening/ identifying autonomic dysfunction in patients before surgery is rather more challenging and has not been systematically explored at scale. The Composite Autonomic Symptom Score-31 (COMPASS-31) score may provide in-depth assessment of autonomic abnormalities in different organs before surgery.[5] This scale includes 31 questions pertaining to mainly six domains of sympathovagal imbalance such as gastrointestinal dysfunction, vasomotor imbalance, secretomotor disturbances, pupillomotor abnormalities, orthostatic intolerance, and urinary dysfunction. The total scoring if added, usually ranges between zero and 100, with a maximum score of 40 for orthostatic intolerance followed by 25 for gastrointestinal dysfunction, 15 for glandular abnormalities, and 10 for urinary ailments with five each for vasomotor and pupillomotor problems, respectively. The scale has an outstanding internal validity of 0.9. However, preoperative COMPASS-31 has not been examined or related to perioperative outcomes including infection and myocardial injury, common complications that prevents recovery and rehabilitation. Moreover, preoperative COMPASS-31 has not been validated against deliverable, objective measures of autonomic dysfunction including heart rate variability.[6]

4.2. Rationale

To provide a mechanistic understanding of why, and which elements of, autonomic dysfunction predisposes individuals to infectious and/or cardiovascular complications following major noncardiac surgery.

4.3. Risks / benefits

This is an observational study and will not involve any interventions that will influence patients care. Blood samples will be obtained at convenient times when routine blood tests are undertaken to minimise patient inconvenience.

5. Study objectives

5.1. Primary objective

- To identify an association between infectious complications and autonomic dysfunction using the preoperative Composite Autonomic Symptom Score-31 scores within 30 days after surgery.

5.2. Secondary objectives

- To identify an association between cardiovascular morbidity and autonomic dysfunction using the preoperative Composite Autonomic Symptom Score-31 scores within 30 days after surgery.

5.3. Mechanistic objectives

- To identify an association between heart rate variability and preoperative Composite Autonomic Symptom Score-31 within the first two days after surgery.
- To explore changes in whole blood proteomics associated with infectious complications 30 days from surgery.

5.4. Primary outcome measure

The primary outcome is the total COMPASS-31 score.

5.5. Secondary outcome measures

Individual components of the COMPASS-31 questionnaire: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, pupillomotor abnormalities.

5.6. Co-exposure of interest

The co-exposure of interest is:

1) Infectious complications within 30 days after surgery, a composite 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:
    i. Superficial surgical site infection;
    ii. Deep surgical site infection;
    iii. Organ space surgical site infection;
    iv. Pneumonia;
    v. Urinary tract infection;
    vi. Laboratory confirmed blood stream infection;
    vii. Infection, source uncertain (antibiotics given on clinical suspicion).

2) Cardiovascular morbidity defined as one or more of Standardised Endpoints and Core Outcome Measures for Perioperative Medicine and Anaesthetic Care (StEP-COMPAC) cardiovascular complications: myocardial infarction, myocardial injury, cardiovascular death, non-fatal cardiac arrest, coronary revascularisation, major adverse cardiac events, pulmonary embolism, deep vein thrombosis, and atrial fibrillation AND/OR hypotension (mean arterial pressure <60mmHg) detected as part of routine clinical care requiring pressor infusion within 30 days after surgery.

5.7. Mechanistic outcome measures

- Myocardial injury by measuring plasma high sensitivity troponin-T (Elecsys, Roche Diagnostics) levels
- Continuous heart rate monitoring using Phillips CE-marked Holter device from the induction of anaesthesia and up to two days after surgery.
- Whole blood proteomic response to ex vivo inflammatory ligands (laboratory work for samples obtained at Royal London Hospital only).

5.8. Process measures

- Duration of hospital stay (number of days from surgery until a participant is medically fit to be discharged from the hospital)
- Critical care admission (level two or level three)
- Duration of critical care days (level two or level three)

6. Study population

During the trial recruitment period, hospital research teams will liaise with clinical staff to identify individuals with upcoming major noncardiac surgery that may be eligible for enrolment. Based on this referral, a member of the team delivering the trial at the hospital (e.g. clinician, nurse or research practitioner) with appropriate knowledge will formally assess eligibility of the participant against trial inclusion and exclusion criteria. No additional tests or investigations will be required for assessing eligibility.

6.1. Inclusion criteria

- Patients aged ≥ 50 years and over undergoing elective major noncardiac surgery under general anaesthesia expected to require at least an overnight stay in hospital.

6.2. Exclusion criteria

- Lack of capacity or refusal to provide written informed consent
- Inability to complete questionnaires
- American Society of Anesthesiologists (ASA) score of I

7. Study design

Multi-centre observational cohort study across surgical services in NHS hospitals.

8. End of study

The end of the study is defined as the point when the last patient has completed the 30-day follow-up.

9. Study procedures

9.1. Screening and recruitment

Research delivery staff at each recruiting site should be regarded as part of the direct care team. Research is a routine part of effective healthcare and will be subject to the same information governance requirements in this respect. Potential participants will be identified via two routes: 1) the direct care team screening pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff or 2) pre-screening patients that have registered their interest in the study via a QR code located on the patient pamphlet. This process requires patients to provide their contact information (i.e. name, telephone number and email address) in a Microsoft form securely stored within QMUL. All patients registered using this method will undergo a further screening by a member of the direct care team to confirm eligibility prior to approach.

All patients who undergo screening will be recorded on the screening log and reasons given for any exclusion. Only anonymised screening data will be collected to allow assessment and reporting of selection bias. Once the participant has been enrolled, they will also be recorded on the study enrolment log together with their study ID. Both the screening and enrolment logs will be stored in the Investigator Site File (ISF).

9.2. Informed consent

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent is duly authorised, trained and competent in obtaining informed consent. All staff taking consent will be trained in taking consent

and this will be evidenced on the local delegation log(s). They will also have appropriate Good Clinical Practice (GCP) training.

The consent process will take place face to face or via a locally approved remote method (phone, video conferencing etc.). All potential participants will be provided with a copy of the latest versions of the patient information sheet and informed consent form together with an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. This will be done either in person (preferred), via email or by post. Where possible all patients will be given a minimum of 24 hours between the time they are approached about the study and the time when consent is given. Prior to consent a member of the research team will confirm how consent will be provided by the patient (face to face, email or post) and this will be documented on the informed consent form itself. For those patients who have not been contacted face-to-face, the signed consent form will be returned via email or by post and counter-signed a member of the research team.

For patients who are consented to participate in the study a copy of the patient information sheet and signed informed consent form will be filed in the medical notes. Patients who are consented but not entered into this study should be recorded (including reason not entered) on the screening log in the Investigator Site File. Original signed consent forms will be kept by the investigators and a copy will be given to the participant. The discussion and the consenting process will be documented in the patients' medical records.

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. The right of a patient to refuse participation without giving a reason will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment.

9.3. Follow-up procedures

Patients will be required to complete the COMPASS-31 questionnaire either face to face or remotely (e.g. phone, post, electronic). For those patients completing the questionnaire electronically, a link or QR code will be sent to them depending on their preference. Once the link has been used, the submitted answers cannot be modified.

Troponin-T will be measured in blood samples collected from venous or arterial catheters before anaesthesia induction and day one after surgery (10:00am ± 6 hours).

Heart rate using the Phillips CE-marked Holter device from before the induction of anaesthesia and up to three days postoperatively. The Holter monitor will be loaned to the sites by the Sponsor.

Participants' medical history will be reviewed to collect the details on surgery and 30-day follow-up which includes any infective and cardiovascular postoperative complications.

9.4. Study schedule

Visit	Screening/ Pre-screening	Before surgery	Day of surgery (Day 0)	Postoperative					Hospital discharge (days + 3 days)	30-day follow-up + 7 days
				Day 1#	Day 2#	Day 3#	Days 4-6	Day 7		
Eligibility	x									
Informed consent		x								
Demographics		x								
Review of medical notes		x								
Data collection		x	x	x	x	x	x	x	x	x
COMPASS 31 questionnaire		x								
Heart rate monitoring			x	x	x					
Blood sample collection			x*	x***						
StEP-COMPAC			x	x	x	x	x	x	x	x
Post-operative infection (Clavien-Dindo Grade II and above)			x	x	x	x	x	x	x	x
Other post-operative complications (Clavien-Dindo Grade II and above)			x	x	x	x	x	x	x	x
Length of hospital stay										x
Hospital readmission										x

* before start of surgery
*** morning after surgery

9.5. Study assessments

The following data will be collected from all patients:

Baseline data

- Study ID
- Patient initials
- Date of consent and surgery
- Age
- Sex at birth
- Planned surgical procedure category
- Co-morbidities
- Frailty (Rockwood scale)
- Ethnicity (to calculate estimated glomerular filtration rate)
- Index of socioeconomic deprivation.
- Laboratory values (haemoglobin, creatinine, neutrophil count, lymphocyte count, albumin)
- Continuous heart rate (measured with Holter monitor) up to three days following surgery
- Planned level of care on the first night after surgery

During surgery

- Start and end times of surgery
- Surgical procedure category (surgery involving the gut, all other surgery)
- Surgical technique (open, laparoscopic, laparoscopic converted to open)
- Anaesthetic technique (general anaesthesia, neuraxial, other regional anaesthesia, sedation)
- Volume of blood products administered (packed red cells, all other products)
- Continuous heart rate (measured with Holter monitor)

Follow-up data

30-day follow-up

- Mortality status within 30 days of surgery
- Clavien-Dindo graded infectious and all-cause complications within 30 days of surgery
- StEP-COMPAC defined cardiovascular complications within 30 days of surgery
- Number of days in level two and level three critical care within 30 days of surgery
- Duration of hospital stay

- Critical care admission
- Duration of critical care days

10. Statistical considerations

10.1. Sample size

296 patients are required to have a 90% chance of detecting, as significant at the 1% level, a mean difference in COMPASS-31 score of 5 (SD:8) between an estimated ~20% patients who develop postoperative infections, compared with patients who remain free of infection after surgery (STATA).

10.2. Method of analysis

For the primary outcome, the absolute COMPASS-31 score will be compared between patients with/without infectious/cardiovascular complications (unpaired t-test). For secondary outcomes, individual components of the COMPASS-31 score, the presence/absence of individual components will be compared (Fisher exact test). Statistical analysis plans for both clinical and mechanistic studies will be published online before database closure.

11. Ethics

The Chief Investigator must ensure that the study is conducted in accordance with the guidelines of the International Conference on Harmonisation, 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.

12. Patient and Public Involvement (PPI)

The grant proposal for this study has been designed with the PPI members at The Patient, Carer & Public Involvement and Engagement (PCPIE) group at the Royal College of Anaesthetists. 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.

13. Data handling and record keeping

13.1. Data management

Data will be transcribed by the local research team at each participating site onto the electronic CRF (eCRF) using on the secure data entry web portal (REDCap). Submitted data will be reviewed for completeness and consistency by authorised users within the trial coordinating team. Submitted data will be stored 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).

13.2. Source Data

In this study, source data will be the information collected in the patient's medical notes.

13.3. Confidentiality

The PI 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 REC Approval. The CI 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.

13.4. Record retention and archiving

During the course of research, the CI 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 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 PI to ensure a full set of records is collated and documented.

14. Laboratories

14.1. Local laboratories

Myocardial injury will be assessed based on serum high sensitivity troponin-T conducted within the William Harvey Research Institute (WHRI) laboratories and Olink proteomics platform.

14.2. 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 analysis. The full sample, collection, labelling, logging and transfer procedure will be documented in the study laboratory log.

14.3. Sample receipt/chain of custody/accountability

Handling of the samples upon arrival at the local and central (WHRI) 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.

14.4. 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 (Chief Investigator), 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 ISF of the participating site.

14.5. Sample and data recording/reporting

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

15. Safety reporting

Due to the nature and design of this study, reporting of safety related events will not occur.

16. 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. In participating hospitals, local study documents may be selected for audit on a local basis. However, the Pero-COMPASS 31 study team will not routinely monitor data collection in individual hospitals or conduct source data verification.

17. Study committees

The Peri-COMPASS 31 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.

18. Finance and funding

The study is part of a PhD project and is funded by King Saud bin Abdulaziz University for Health Sciences and Queen Mary University of London. The funders will play no role in study design, conduct, data collection, data analysis, reporting or interpretation of the results.

19. Insurance and indemnity

The insurance that Queen Mary 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.

20. 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 Peri-COMPASS 31 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.

21. References

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3. Abbott TEF, Pearse RM, Cuthbertson BH, Wijeysundera DN, Ackland GL, METS study investigators. Cardiac vagal dysfunction and myocardial injury after non-cardiac surgery: a planned secondary analysis of the measurement of Exercise Tolerance before surgery study. Br J Anaesth. 2019 Feb;122(2):188–97.

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5. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc. 2012 Dec;87(12):1196–201.

6. James A, Bruce D, Tetlow N, Patel ABU, Black E, Whitehead N, et al. Heart rate recovery after orthostatic challenge and cardiopulmonary exercise testing in older individuals: prospective multicentre observational cohort study. BJA Open. 2023 Dec;8:100238.