Targeted heart rate control using the funny current inhibitor ivabradine to reduce morbidity in patients undergoing non-cardiac surgery: a phase IIa, triple blind, placebo controlled randomised trial (FUNNY).

Statistical Analysis Plan (SAP)

IRAS reference 1003561

Sponsor Number 012663

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Statistician Signature:

Version History

SAP Version	Protocol Version	Date	Reason for revision	Summary of changes made
0.1 (draft)	**4.0**	**22/01/2025**	First draft	
0.2 (draft)	**4.0**	**10/03/2025**	Second draft review by the team	Changes to summary table, clarifying definitions, references correction, Dummy tables
0.3 (draft)	**4.0**	**19/05/2025**	Definition of secondary outcomes	
0.4 (draft)	**4.0**	**6/6/2025**	Corrections made to previous drafts by **CI.**	Additional dummy tables as per CRF; corrections to existing tables; addition of relevant appendices; formatting.
0.5 (draft)	**4.0**	**13/06/2025**	Corrections made to previous drafts by **CI.**	Additional dummy tables as per CRF; corrections to existing tables; formatting.
1.0	**4.0**	**22/08/2025**	Corrections made to previous drafts by CI and statistician, first approved version Addition of new statistician	Corrections to existing tables; formatting.
2.0	**5.0**	**18/11/2025**	Corrections agreed by CI and statistician. Updated protocol version.	Exploratory analysis of dynamic HR changes in first 72h during dosing, in relation to primary and secondary outcomes. Addition of updated protocol version which includes minor

				changes as follows: 1. Study duration has been extended to allow for completion of target recruitment 2. Removal of previous statistician and addition of new statistician 3. Clarifications to parts of the protocol that does not affect the scientific value of the trial 4. Correction of typographical errors 5. Removal of a non-participating sites and hospitals from the protocol 6. SmPC updated with renewal of authorisation date 7. Update to Sponsor address

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1. Summary of the trial

Full Title	Targeted heart rate control using the funny current inhibitor ivabradine to reduce morbidity in patients undergoing non-cardiac surgery: a phase IIa, triple blind, placebo-controlled randomized trial
Short Title	FUNNY
Study objectives	To determine whether targeted lowering of heart rate with ivabradine during the perioperative period reduces morbidity associated with myocardial injury within seven days of elective or urgent non-cardiac surgery. Secondary objectives: To examine the relationship between selective heart rate reduction in relation to preoperative heart rate and myocardial injury and severity of complications (Clavien-Dindo graded POMS defined morbidity).
Chief Investigator	Professor Gareth Ackland
IRAS reference	1003561
Sponsor Number	012663
EudraCT Number	2020-002099-11
Trial Design and Methodology	Triple-blind, placebo-controlled randomized trial
Phase of the Trial	Phase IIa
Study Duration	55 months
Study Setting	Hospitals undertaking elective or urgent non-cardiac surgery in participating countries
Number of Patients	350 patients (175 patients per treatment arm)
PICOT Summary	
Population	Patients aged 55 years and over undergoing elective or urgent non-cardiac surgery
Intervention	Targeted heart rate control with ivabradine initiated before surgery and continuing for 72 hours post-surgery. Dosing will be adjusted based on heart rate measurements.
Comparator Intervention	Placebo initiated before surgery and continuing for 72 hours post-surgery, with adjustments mimicking the active treatment arm
Primary Outcome Measure	Composite of myocardial injury associated with morbidity within seven days of surgery. **Criteria:** 1. Increase in serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) concentration: - Absolute value ≥15 ng/L on day 1, 2, or 3 **OR** - Increase of ≥5 ng/L from preoperative value on day 1, 2, or 3 when preoperative value was ≥15 ng/L **AND** 2. Any POMS-defined morbidity domain recorded on day 3 or day 7 after surgery.
Secondary outcome	(1) Peak value of Troponin-T measured within 48 hours of surgery. Peak Troponin-T (ng/L) will be calculated as the maximum values from the blood samples collected at 24 hours and 48 hours after surgery. (2) Any POMS defined morbidity domain on day three or seven after surgery (3) Mortality within 180 days from surgery (4) Predefined complications at day 30 after surgery graded using the Clavien-Dindo classification.
Maximum Treatment Duration	Three days
Follow-Up Duration	180 days from the day of surgery
End of Trial Definition	When the last patient has completed their 180-day follow-up.

2. Background

At least 300 million surgical operations are estimated to occur each year globally[1]. Myocardial injury after non-cardiac surgery occurs in approximately 40% of high-risk older patients with comorbidities undergoing elective major surgery [2].

Myocardial injury is defined by significant elevations in troponin levels using high-sensitivity assays[3] and is associated with short-term morbidity and longer-term complications, including mortality [4–7].
Several factors contribute to myocardial injury

(1) Supply-demand mismatch due to hemodynamic instability [8,9] and tachycardia. [10,11]

(2) Higher preoperative heart rates (>83 bpm) are independently associated with myocardial injury.[10,11]

(3) Vagal autonomic dysfunction may promote cardiovascular injury and multi-organ dysfunction. [12,13].

Previous attempts to limit tachycardia using beta-blockers and clonidine resulted in hypotension and ischemic stroke. The POISE-1 trial highlighted the dangers of using fixed-dose, extended-release beta-blockers without titration or individualised dosing [14,15].
In contrast, ivabradine, a specific funny channel (I(f)) current inhibitor located in the sino-atrial node of the heart, reduces heart rate without altering autonomic control, myocardial contractility, or blood pressure [16]. These properties have made ivabradine useful in chronic heart failure and acute cardiac care, where it effectively reduces heart rate without haemodynamic compromise [17].

3. Study Rationale

The FUNNY trial hypothesises that targeted heart rate control with ivabradine for the first 72 hours of the perioperative period will reduce early myocardial injury and subsequent morbidity. This effect may be more pronounced in participants with poor baseline cardiovascular function (high preoperative NT-proBNP), vagal autonomic dysfunction (higher preoperative resting heart rate, impaired orthostatic heart rate response).
Key points supporting this rationale include:

(1) Surgical patients with multi-morbidity at highest risk of postoperative complications often have profound parasympathetic dysfunction [4,18–20].

(2) Preoperative impairment of parasympathetic (vagal) autonomic function is a sole predictor of perioperative myocardial injury, postoperative infections, and death [21].

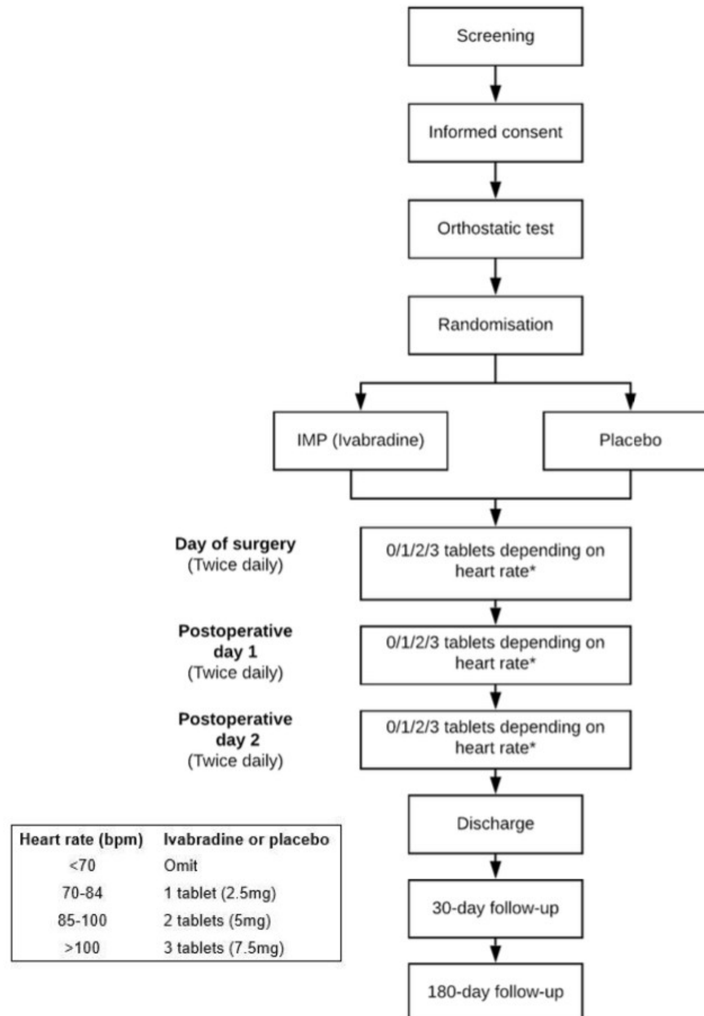
(3) Impaired neuro-cardiovascular control contributes to intraoperative hypotension, which is repeatedly associated with adverse outcomes [22,23].

(4) Ivabradine's mechanism of action, which involves inhibiting the funny channel HCN4, mimics the beneficial effects of sustained exercise training on heart rate [24–26].

(5) Unlike beta-blockers, ivabradine does not impair myocardial contractility, affect blood pressure, or impair sympathetic nervous activity, even in patients with cardiac failure [16].

By investigating the impact of ivabradine on perioperative outcomes, this study aims to provide insights into the role of heart rate control in reducing postoperative complications and improving patient outcomes after non-cardiac surgery, particularly in high-risk populations with autonomic dysfunction.

4. Trial Flowchart



5. Objectives

Primary Objective

To determine whether the targeted lowering of heart rate with ivabradine during the perioperative period reduces morbidity associated myocardial injury within seven days of elective or urgent non-cardiac surgery.

Secondary Objective

To examine the relationship between selective heart rate reduction and severity of Clavien-Dindo graded complications and Postoperative Morbidity Survey (POMS) defined morbidity.

6. Outcome measures

Primary outcome measure

A binary categorical variable (1 or zero), which is a composite of myocardial injury **associated with** morbidity within seven days after surgery.

To meet the criteria for the primary outcome (=1), the patient must experience myocardial injury after surgery (MINS) defined using the VISION study criteria.[3]:

(1) Increase in serum high sensitivity troponin-T concentration of an absolute value of ≥15ng L^{1} on any of day one, two or three after surgery, provided the preoperative value was <15ng L-^{1} OR, if the preoperative value was ≥15ng L-^{1,} an increase of ≥5 ng L^{-1} on day one, two or three after surgery compared to the preoperative value.

AND:

(2) any POMS defined morbidity domain (see Appendix A) being **present** within seven days after surgery after surgery (binary categorical variable: present=1 or absent=zero).

Secondary Outcome measures

We will report individual components of the composite primary outcomes as secondary outcomes.

(1) Peak value of Troponin-T measured within 48 hours of surgery. Peak Troponin-T (ng/L) will be calculated as the maximum value from the blood samples collected at 24 hours and 48 hours after surgery.

(2) Mortality within 180 days from surgery (binary categorical variable: dead=1, alive =0)

(3) Pre-defined complications at day 30 after surgery (Appendix B), graded ≥2 using the Clavien-Dindo classification* (binary categorical variables: present=1 or absent=zero)

*Graded according to clinical criteria, see appendix C.

7. Process Measures

1) Duration of hospital stay (in days) after surgery (Number of calendar days from surgery until hospital discharge, where the day of surgery is day 0)

2) Number of calendar days requiring critical care admission (level two and three) up to 30 days from surgery (where any time <24 hours is counted as one day; 24-48 hours is two days etc).

3) Re-admission to hospital within 30 days of surgery will be presented as number (%).

8. Assessment of Primary and Secondary Outcomes

(1) Blood samples will be collected to measure troponin-T levels:

- Before induction of anaesthesia,
- On days one, two, and three after surgery.

(2) POMS and pre-defined Clavien-Dindo graded complications will be assessed by an investigator not involved in patient care and unaware of treatment group allocation

(3) Assessment will be based on clinical data, including medical records, test results, drug charts.

(4) Patients discharged before day 30 will be contacted to ascertain if they have received any new treatments or have been readmitted to hospital

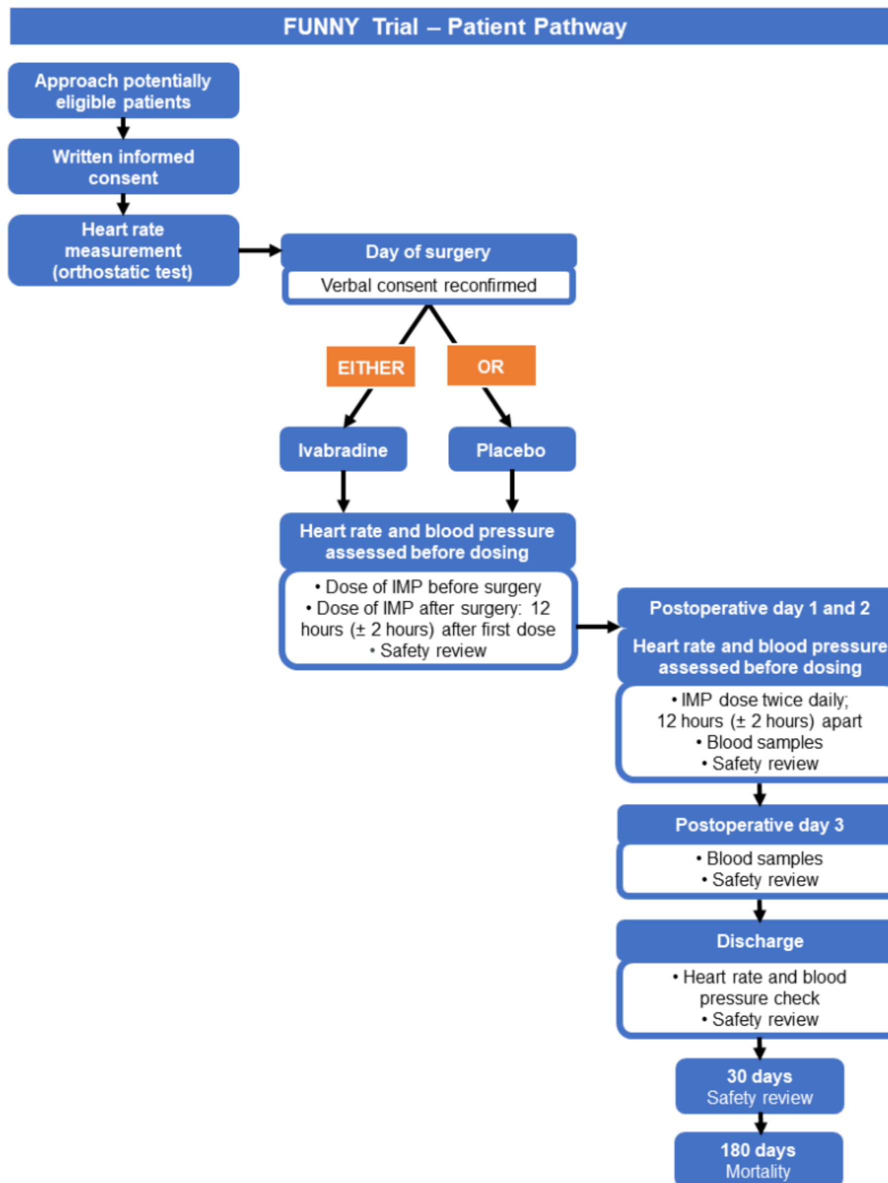
(5) Mortality status will be confirmed at 180 days from surgery

(6) For complications, defined by POMS and Clavien-Dindo), the initial assessment by a research associate will be confirmed by the site Principal Investigator.

9. Trial Methodology

Study Design

The FUNNY trial is a phase IIa, triple-blind, placebo-controlled randomised trial investigating the effect of targeted heart rate control using ivabradine on morbidity in patients undergoing non-cardiac surgery.



10. Study setting

The trial will be conducted in hospitals undertaking elective or urgent non-cardiac surgery in participating countries. Specific sites include:

- Barts Health NHS Trust (Royal London Hospital), England
- Hôpitaux Universitaires de Genève, Geneva, Switzerland.
- NHS Golden Jubilee Hospital, Glasgow, Scotland.

11. Eligibility Criteria

All patients must meet all the inclusion criteria and none of the exclusion criteria, as below.

Inclusion Criteria

(1) Patients aged 55 years and over

(2) Undergoing elective or urgent non-cardiac surgery requiring general and/or regional anaesthesia with sedation, expected to take longer than 120 minutes from induction of anaesthesia

(3) At least one medical risk factor for perioperative myocardial injury. Refer to Appendix A in the main protocol, which may include a history of hypertension (requiring anti-hypertensive drugs) or hypertension recorded in pre-assessment clinic (BP >. 140 mmHg systolic; >90 mmHg diastolic).

Exclusion Criteria

(1) Inability or refusal to provide informal consent

(2) Patients lacking capacity

(3) Patients with atrial fibrillation

(4) Prior use of ivabradine within the previous 30 days

(5) Current participation in a clinical trial of a treatment with a similar biological mechanism

(6) Previous enrolment into FUNNY trial

(7) Contraindication to ivabradine (See Appendix D in the protocol v4.0)

(8) History of hypersensitivity or allergy to ivabradine or any of its excipients

(9) Women of childbearing potential (defined as a premenopausal female capable of becoming pregnant unless permanently sterile).

12. Randomisation

Randomisation will occur on the day of surgery but before the surgery is due to start (Datameld bespoke software, R Hewson). Before randomisation consent must be obtained and it must be confirmed with the lead anaesthetist and/ or surgeon on the day of surgery that the procedure will go ahead. Participants will be centrally allocated to treatment groups in a 1:1 ratio by minimisation with a random component.

Minimisation variables are (1) surgical procedure category (surgery involving the gut *OR* all other surgery); (2) trial site.

Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. 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.

When participants are randomised according to the incorrect surgical procedure category, under the intention to treat 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[28] .

13. Statistical and data analysis

Sample size calculation

The total sample size is 350 patients with 175 participants assigned randomly to each arm. This will include a dropout rate of 1%. This sample size is based on VISION-UK data which showed that morbidity associated with troponin elevation (≥15ng L) in the first 24 hours after surgery is experienced by 59% of patients with similar characteristics.[27] By contrast, 41% of patients without any troponin elevation sustained postoperative morbidity, representing a 31% lower relative risk of morbidity after surgery compared to patients who sustained myocardial injury defined by elevation in troponin. Assuming a conservative relative risk reduction of 25%, 173 patients will be required in each arm if ivabradine reduces the incidence of myocardial injury-associated morbidity from 59% (placebo) to 44% (α=0.05; 1-β=0.8).

Summary of baseline data and flow 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, which will summarise the flow of patients through the trial, including the number of patients screened, excluded, eligible, randomised, those not receiving the drug/placebo and analysed for each outcome. Baseline characteristics and clinical data defined by the protocol will be summarised by treatment groups. Continuous variables will be presented as mean (SD) or median (IQR) as appropriate. Categorical variables will be presented as frequency (%). No formal statistical comparison of baseline characteristics between groups will be performed as per CONSORT guidelines.

Characteristics of the cohort, presented by trial group (table 1).

We will report a summary of descriptive data stratified by the treatment group in table format. Continuous data will be presented as mean (SD) or median (IQR) and categorical data will be presented as number (%). Hypothesis testing will not be conducted on baseline data (tables 1-4).

The following characteristics will be presented, compared between ivabradine versus placebo groups.

- Age, mean (SD) and median (IQR)
- Sex, n (%)
- Smoking status (within past 14 days)

- Surgical procedure category (Surgery involving gut, all other types)
- Ethnicity
- Comorbidities
- Cardiovascular medications

Clinical management for the ivabradine and placebo groups will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group.

Intraoperative data, compared between ivabradine versus placebo groups (table 2).

- Heart rate measurements specifically tachycardia.
- Blood pressure measurements during surgery- Systolic blood pressure <90mmHg
- Surgical technique (Open, laparoscopic or laparoscopic assisted, laparoscopic converted to open).
- Anaesthetic technique (general anaesthesia, epidural, spinal, other regional anaesthesia, sedation)
- Endotracheal intubation for surgery

Post-operative data for day of surgery and days 1, 2 and 3 after surgery, compared between ivabradine versus placebo groups. (Table 3).

- Level of care (ward/critical care)
- Blood products (ml)
- Urine output (ml), if recorded.
- Heart rate >100bpm (yes/no; n, %), with highest value (bpm), duration >100bpm (min), intravenous fluids (yes/no; n, %), and need for pharmacological therapy recorded (yes/no; n, %).
- Systolic blood pressure <90mmHg (yes/no; n, %).
- Vasopressor support (yes/no; n, %), Phenylephrine, ephedrine, metaraminol, norepinephrine and Other pressor support.
- Cardiovascular medications

Heart rate and IMP administration, compared between ivabradine versus placebo groups (Table 4).

Heart rate (median (IQR) before drug administration and on postoperative days 1 and 2 along with the number of tablets administered (0/1/2/3 tablets) and prescribed- but not given- doses will be presented.

Primary outcome analysis (Table 5), incorporating postoperative morbidity (Table 6).

The primary outcome is a composite of myocardial injury associated with morbidity *(Table 6)* within seven days of surgery. The analysis will be performed on an intention-to-treat basis, including all randomised patients in the group to which they were allocated. The primary outcome will be compared between treatment groups using a chi-squared test. The effect size will be reported as a risk ratio with 95% confidence interval. A mixed effect logistic regression model will be used to adjust for the minimisation variables (surgical procedure category and trial site).

The model will also be adjusted for pre-specified baseline covariates entered into the model as fixed factors and trial sites as a random effect variable. Preoperative heart rate will be included as a continuous variable, assuming a linear association with the outcome. The magnitude of treatment effect will be reported as an adjusted odds ratio with a 95% confidence interval. Significance will be set at $p < 0.05$.

Secondary outcome analysis (Table 5)

Binary secondary outcomes

Binary secondary outcomes including MINS (myocardial injury after surgery), any POMS-defined morbidity (Table 6), mortality at 180 days, and predefined complication (e.g., Clavien-Dindo classification) will be analysed using mixed-effect logistic regression models. These models will include the trial site as a random effect to account for clustering within sites and will adjust for fixed effects such as surgical procedure category and other relevant covariates. Results will be presented as odds ratios with 95% confidence intervals.

Continuous secondary outcomes

Peak level of Troponin-T within 48 hours of surgery will be presented as mean (SD) within each treatment group. Differences between the groups in the mean peak level troponin-T will be analysed using linear mixed-effect models. Trial site will be included as a random effect to account for between-site variability, and fixed effects will include surgical category and other covariates. The model will also be adjusted for baseline pre-operative Troponin-T. Results will be presented as mean difference with 95% confidence intervals.

14. Other analyses, data summaries and graphs

Process measures (Table 7)

Summary measures will be presented separately for each treatment group. All patients with recorded data will be included in the summary. Formal statistical analysis will not be performed. Duration of

hospital stay after surgery (days) and total duration of critical care stay within 30 days of surgery (days) will be summarised using mean (SD) and median (IQR). Re-admission to hospital within 30 days of surgery will be presented as number (%).

Adverse events: safety analyses (Table 8 and 9)

Pre-specified adverse events and 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. (Table 10)

Numbers and percentages of protocol deviations will be reported. Prescribed but not administered doses will be reported (Table 4). In addition to this, 'other' protocol deviations will be reported separately of prevalence is more than 5% in the trial.

Serial haematological and biochemical profiles (Table 11)

If measured, serial measures of haemoglobin (g/L), creatinine (μmol/L), neutrophil count (10^9L) lymphocyte count (10^9L), albumin (g/L) will be presented as mean (SD) and median [IQR], but not subject to any statistical comparison.

Complications within 30 days after surgery (Table 12)

The number and percentage of patients experiencing each of the following complications will be presented by treatment allocation. These summaries will not be subjected to any statistical testing. These complications are as follows: Cardiac complications, Respiratory complications, Infective complications, other complications and Acute kidney injury.

15. Prespecified Subgroup analysis.

Subgroup analyses will be performed for the primary outcome to assess whether the effect of targeted heart rate control with ivabradine differs among patients at the highest risk of myocardial injury, as predicted from preoperative higher heart rate. The following subgroups will be analysed:

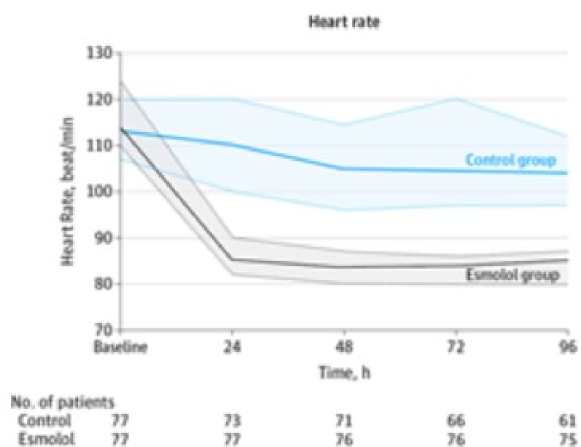
Preoperative NT-proBNP

Patients with elevated preoperative plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP >100 pg ml^{-1}) experience more complications after noncardiac surgery.[22] The primary analysis will be run for patients with NT-proBNP >100 pg ml^{-1} compared to those with NT-proBNP <=100 pg ml.

Exploratory analyses of dynamic Heart-rate metrics and outcomes.

Two complementary heart-rate measures will be evaluated to explore their association with the 7-day primary and secondary outcomes. First, **pre-operative tachycardia** is defined a priori as a resting HR > 83 bpm, based on prior perioperative studies linking this threshold to autonomic dysfunction and adverse outcomes. [10,11,22]. This binary categorical variable will be entered into the adjusted model alongside treatment group, age, sex, ischaemic heart disease, surgery type, and centre. Cumulative ivabradine doses will be reported for each group. Second, to characterise **postoperative HR dynamics** and the impact of heart rate changes (either due to ivabradine or intrinsic patient physiology) on the primary and secondary outcomes, the cumulative dose of ivabradine and area-under the curve of HR will be calculated for each patient over the first 60h after surgery. A model will be presented using the area under the curve of HR (AUC ΔHR per 24 h)—that serves as a continuous predictor, adjusted for age, gender, surgical procedure, pre-operative heart rate </>83bpm, IHD, diabetes, congestive heart failure, CVA, eGFR(<59ml/min/1.73m^2), PVD and hypertension as fixed effects and centre as a random effect. These analyses will be performed to distinguish the prognostic effects of baseline tachycardia from those of achieved and/or sustained postoperative HR control, with results reported as adjusted risk ratios (RR) and 95 % confidence intervals. A figure showing the effect of ivabradine dosing versus no dosing [either placebo or 0mg in the active arm] at each timepoint will be plotted [see figure opposite; doi:10.1001/jama.2013.278477].

The association between pre-op HR </>83 bpm and postoperative HR (AUC ΔHR) will also be plotted, with treatment stratification (placebo vs ivabradine). This analysis will show whether patients who started with relative tachycardia achieved (or failed to achieve) the same degree of HR lowering postoperatively.



16. Statistical Approach for Subgroup Analysis

Troponin positivity and POMS defined morbidity outcome

For the secondary POMS outcome, we will assess the impact of troponin positivity on outcome separately in placebo and ivabradine groups. This will be done by including a troponin by treatment interaction term in the logistic model for POMs morbidity. A significant interaction term will indicate a difference in the troponin effect between treatments.

Interaction Terms

Subgroup analyses will include interaction terms between treatment allocation (ivabradine vs. placebo) and subgroup variables in the logistic regression model for the primary outcome.
The presence of significant interaction terms will indicate whether the treatment effect differs across subgroups.

Mixed-Effects Models

Mixed-effects logistic regression models will be used, including trial site as a random effect to account for clustering within sites.

Effect Estimates

For each subgroup, the treatment effect (odds ratio) and its 95% confidence interval will be reported.
Forest plots will be used to visually present treatment effects across subgroups.

17. Missing data and sensitivity analysis

Missing data for the primary outcome will be handled using multiple imputation, assuming data are missing at random. The amount of missing primary outcome data is anticipated to be minimal but will be accounted for in a sensitivity analysis if missing data is greater than 5%. The primary analysis will be repeated once assuming that all patients in the intervention group with missing outcomes did not experience myocardial injury, and all patients in the placebo group with missing outcomes experienced myocardial injury. The analysis will then be repeated with the opposite assumptions. This will then give the absolute range of how much the results could change if the data were complete. This will also assess the robustness of our analysis of the primary outcome under the assumption that data is missing-not-at random.

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Figure 1: CONSORT Flow Diagram for both primary analysis and 180-day follow-up.

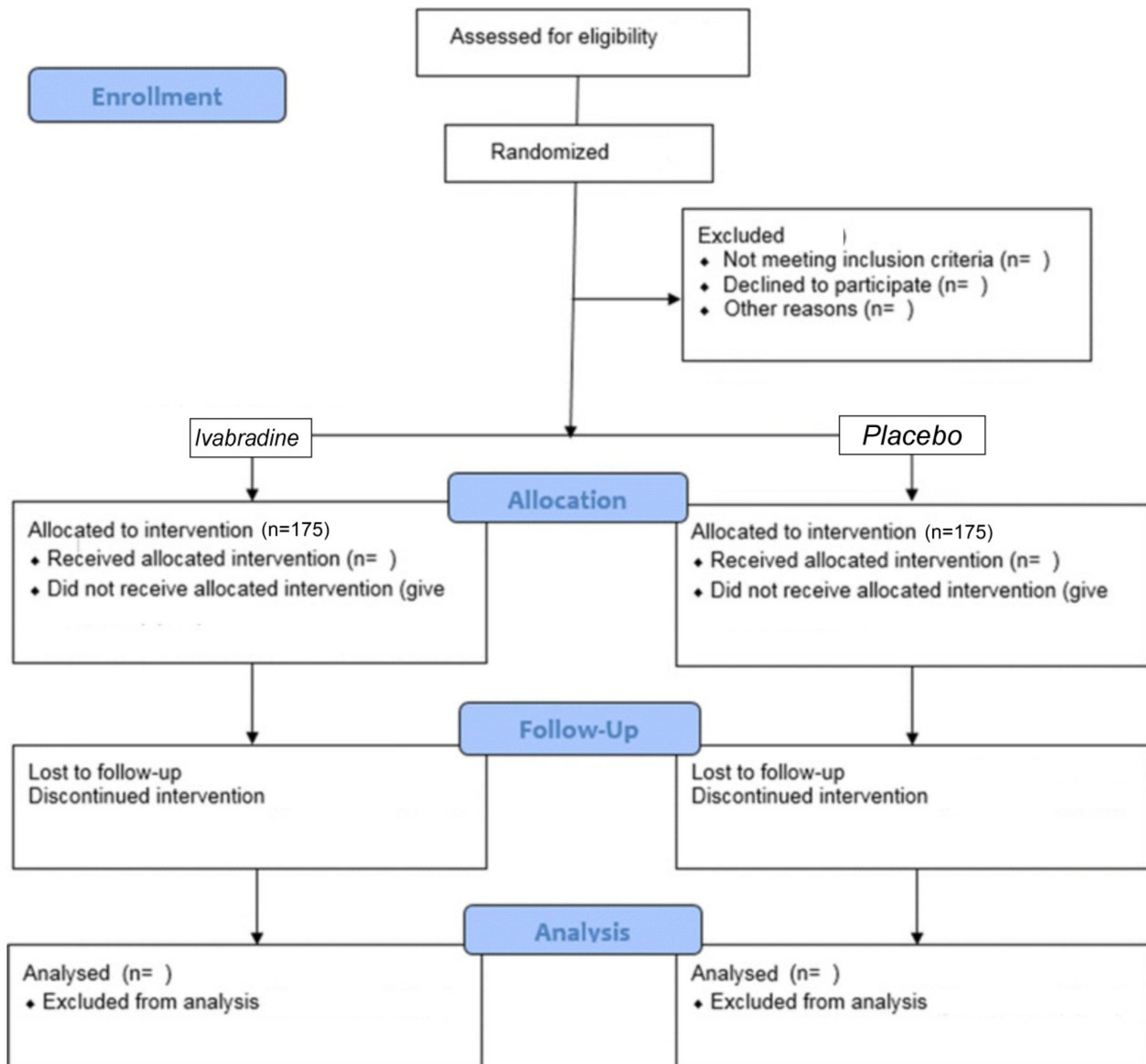

Table 1: Baseline characteristics.

Baseline Characteristics	Number of patients with available data - no. (%)		Summary measure	
	Ivabradine (n=xxx/XXX)	**Placebo** (n=xxx/XXX)	**Ivabradine**	**Placebo**
Sex - (n, %)				
Male				
Female				
Age (years)				
Mean (SD)				
Median (IQR)				
Ethnicity - (n, %)				
White				
Mixed or Multiple ethnic groups				
Black, African, Caribbean or Black British				
Asian or Asian British				
Other				
Height (cm)				
Weight (kg)				
Body mass index (kg.m^2)				
Current smoker (within last 14 days) (n, %)				
Chronic comorbid disease - (n, %)				
Chronic Obstructive Pulmonary Disease				
Asthma				
Interstitial lung disease or pulmonary fibrosis				
Ischaemic heart disease				
Congestive heart failure				
Diabetes mellitus (type I or II)				
Liver cirrhosis				
Active cancer				
Stroke or transient ischaemic attack				

Peripheral vascular disease				
Hypertension				
Planned Surgical Procedure (n, %)				
Surgery involving the gut				
All other surgery				
Participating Site (n, %)				
Barts Health NHS Trust (Royal London Hospital), England				
Hôpitaux Universitaires de Genève, Geneva, Switzerland				
NHS Golden Jubilee Hospital, Glasgow, Scotland				
Surgical procedure performed (n, %)				
Surgery involving the gut				
All other surgery				
Pre-operative blood test results				
Haemoglobin ($g.l^{-1}$)				
Mean (SD)				
Median (IQR)				
Creatinine ($\mu mol\ l^{-1}$)				
Mean (SD)				
Median (IQR)				
Estimated GFR (ml.min.1.73m²)*				
Neutrophil count ($n.10^9\ l^{-1}$)				
Lymphocyte count ($n.\ 10^9\ l^{-1}$)				
Neutrophil/lymphocyte ratio				
Albumin ($g.l^{-1}$)				
NT-proBNP ($pg.ml^{-1}$)				
>100$pg.ml^{-1}$ (n; %)				
Cardiometabolic medications (n, %)				
ACE-I				
ARB				
Beta blocker				
Calcium channel antagonist (for blood pressure)				

Heart rate limiting calcium channel antagonist (verapamil/diltiazem)				
Doxazosin				
Diuretic				
Statin				
Nitrate				
Anti-platelet agents				
Warfarin				
DOACs (e.g. dabigatran, apixaban)				
Any other anticoagulation established pre-operatively (e.g. LMWH)				
Metformin				
Insulin				
Any other diabetic medication				

**Estimated GFR calculated by CKD-EPI calculation (2021).*

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funny

Table 2: Intraoperative Clinical Management.

Clinical management	Number of patients with available data - no. (%)		Summary measure	
	Ivabradine (n=xxx/XXX)	**Placebo** (n=xxx/XXX)	**Ivabradine**	**Placebo**
Surgical Technique (n, %)				
Open surgical technique used during surgery				
Laparoscopic or laparoscopic assisted technique				
Laparoscopic converted to open				
Anaesthetic technique (n, %)				
General anaesthesia alone				
General + epidural anaesthesia				
General + spinal anaesthesia				
General + other regional anaesthesia				
Regional anaesthesia with sedation				
Endotracheal tube inserted				
Duration of surgery (mins)				
Planned level of care on the first night after surgery (n, %)				
Surgical ward				
Critical care level 2				
Critical care level 3				
Post-anaesthesia care unit				
Blood pressure during surgery				
Systolic blood pressure <90mmHg during surgery (n, %)				
Vasopressor support required. (n, %)				
Phenylephrine				
Ephedrine				
Metaraminol				
Norepinephrine				
Other pressor support - no. (%)				
Intravenous fluids during surgery				

Fluid administered, excluding blood products (%)				
Total volume of blood products administered (mL)				
Median (IQR)				
Heart rate >100bpm (n, %)				
highest value (bpm)				
Duration (min)				
intravenous fluids (n; %)				
pharmacological therapy (n; %)				

Table 3: Postoperative clinical management (day of surgery and days 1-3 after surgery).

Postoperative clinical management	Number of patients with available data - no. (%)		Summary measure	
	Ivabradine (n=xxx/XXX)	**Placebo** (n=xxx/XXX)	**Ivabradine**	**Placebo**
Postoperative day of surgery				
Level of care (ward/critical care (n:%)				
Blood products (ml)				
Urine output (ml), if recorded.				
Heart rate >100bpm (n, %)				
highest value (bpm)				
Duration (min)				
intravenous fluids (n; %)				
pharmacological therapy (n; %)				
Systolic blood pressure <90mmHg (n, %)				
Vasopressor support (n, %)				
Phenylephrine				
Ephedrine				
Metaraminol				
Norepinephrine				
Other pressor support - no. (%)				
Postoperative day 1				
Level of care (ward/critical care (n:%)				
Blood products (ml)				
Urine output (ml), if recorded.				
Heart rate >100bpm (n, %)				
highest value (bpm)				
Duration (min)				
intravenous fluids (n; %)				
pharmacological therapy (n; %)				

Systolic blood pressure <90mmHg (n, %)				
Vasopressor support (n, %)				
Phenylephrine				
Ephedrine				
Metaraminol				
Norepinephrine				
Other pressor support - no. (%)				
Cardiometabolic medications (n, %)				
Postoperative day 2				
Blood products (ml)				
Urine output (ml), if recorded.				
Heart rate >100bpm (n, %)				
highest value (bpm)				
Duration (min)				
intravenous fluids (n; %)				
pharmacological therapy (n; %)				
Systolic blood pressure <90mmHg (n, %)				
Vasopressor support (n, %)				
Phenylephrine				
Ephedrine				
Metaraminol				
Norepinephrine				
Other pressor support - no. (%)				
Cardiometabolic medications (n, %)				
Postoperative day 3				
Blood products (ml)				
Urine output (ml), if recorded.				
Heart rate >100bpm (n, %)				
highest value (bpm)				
Duration (min)				

intravenous fluids (n; %)				
pharmacological therapy (n; %)				
Systolic blood pressure <90mmHg (n, %)				
Vasopressor support (n, %)				
Phenylephrine				
Ephedrine				
Metaraminol				
Norepinephrine				
Other pressor support - no. (%)				
Cardiometabolic medications (n, %)				

Table 4: Heart rate and IMP administration.

Heart rate –median (IQR); number of tablets n (%) for 0/1/2/3 tablets. 1 tablet=2.5mg, 2 tablets=5mg, 3 tablets=7.5mg.

	Ivabradine (# of patients with available data; n (%))	**Placebo** (# of patients with available data; n (%))
Total number of doses (n)		
Before surgery: heart rate (bpm)	Median (IQR)	Median (IQR)
- number of tablets given	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)
- *doses prescribed but not given, n (%)*		
After surgery: heart rate (bpm)	Median (IQR)	Median (IQR)
-number of tablets given	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)
rescue treatment for bradycardia, n (%)	n (%)	n (%)
doses prescribed but not given, n (%)		
Day 1 after surgery –AM: heart rate (bpm)	Median (IQR)	Median (IQR)
-number of tablets given	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)
rescue treatment for bradycardia, n (%)	n (%)	n (%)
doses prescribed but not given, n (%)		
Day 1 after surgery –PM: heart rate (bpm)	Median (IQR)	Median (IQR)

-number of tablets given	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)
rescue treatment for bradycardia, n (%)	n (%)	n (%)
doses prescribed but not given, n (%)		
Day 2 after surgery –AM: heart rate (bpm)	Median (IQR)	Median (IQR)
-number of tablets given	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)	**Zero:** n (%) **One:** n (%) **Two:** n (%) **Three:** n (%)
rescue treatment for bradycardia, n (%)	n (%)	n (%)
doses prescribed but not given, n (%)		
Day 2 after surgery –PM: heart rate (bpm)	Median (IQR)	Median (IQR)
rescue treatment for bradycardia, n (%)	n (%)	n (%)
doses prescribed but not given, n (%)		

Table 5: Primary and secondary outcomes.

1. Troponin-T ≥15 ng/L on days 1, 2 or 3 after surgery with a pre-operative value <15 ng/L *OR* Troponin-T increase ≥5 ng/L on day 1, 2 or 3 after surgery with a pre-operative value ≥15ng/L; 2. defined by Post Operative Morbidity Survey; 3. Clavien Dindo defined complications up to 30 days after surgery.

Outcomes	**Number of patients with available data - no. (%)**		**Summary measure**		**Treatment effect Odds ratio (95% CI)**	**P-value**
	Ivabradine (n = xxx/XXX)	**Placebo (n = xxx/XXX)**	**Ivabradine**	**Control**		
Primary outcome						
Myocardial injury associated with morbidity within 7 days of surgery (n; %)						
Secondary outcomes						
					Treatment effect Mean difference (95% CI)	
Peak level Troponin-T ($ng.ml^{-1}$)						
					Treatment effect Odds ratio (95% CI)	
Troponin increase meeting MINS criteria (n; %)[1]						
Morbidity within 7 days after surgery (n; %)[2]						
Clavien Dindo defined complications *grade ≥ II* (n; %)[3]						
Mortality at 180 days (n; %)						

Table 6. Post Operative Morbidity.

	Day 3 after surgery		**Day 7 after surgery**	
	Ivabradine (n = xxx/XXX)	**Placebo** (n = xxx/XXX)	**Ivabradine** (n = xxx/XXX)	**Placebo** (n = xxx/XXX)
Pulmonary (n; %)				
Infectious (n; %)				
Renal (n; %)				
Gastrointestinal (n; %)				
Cardiovascular (n; %)				
Neurological (n; %)				
Wound (n; %)				
Haematological (n; %)				
Pain (n; %)				
Mobility (n; %)				

Definitions in Appendix A.

Table 7: Process measures.

Process measures	Number of patients with available data - no. (%)		Summary measure	
	Ivabradine (n=xxx/XXX)	**Placebo (n=xxx/XXX)**	**Ivabradine**	**Placebo**
Re-admission to hospital within 30 days of surgery (n, %)				
Duration of primary hospital admission (from surgery)				
Mean (SD)				
Median (IQR)				
Admitted to critical care (n, %)				
Total duration of critical care stay within 30 days of surgery				
Mean (SD)				
Median (IQR)				

Table 8: Adverse events

Adverse Events - no. (%)	Summary measure	
	Ivabradine (n = xxx/XXX)	**Placebo** (n = xxx/XXX)
Patients with ≥ 1 adverse event	n; %	n; %
Total number of adverse events	n; %	n; %
Number of adverse events per patient		
0	n; %	n; %
1	n; %	n; %
2	n; %	n; %
3	n; %	n; %
Type of adverse event (n, %)		
Bradycardia requiring rescue therapy/pacing.[1]		
Atrial fibrillation.[2]		
Tachycardia requiring treatment.[3]		
Hypotension requiring pressor infusion.[4]		
Phosphenes		
Other		

1. *<45bpm, detected as part of routine clinical care within the first 6 postoperative days.*
2. *detected as part of routine clinical care within the first 6 postoperative days.*
3. *>100bpm sinus rhythm, detected as part of routine clinical care within the first 6 postoperative days.*
4. *Hypotension defined as MAP<60mmHg, detected as part of routine clinical care within the first 6 postoperative days.*

Table 9: Serious Adverse events

Serious adverse events - no. (%)	Summary measure	
	Ivabradine (n = xxx/XXX)	**Placebo (n = xxx/XXX)**
Patients with ≥1 Serious adverse events		
Total number of SAEs		
Type of SAEs		
Death		
Life-threatening complication		
Prolonged existing hospital stay or required re-admission		
Significant disability or incapacity		
Other important medical event		

Table 10: Protocol deviations

Protocol deviations - no. (%)	Summary measure	
	Ivabradine (n = xxx/XXX)	**Placebo (n = xxx/XXX)**
Patients with ≥1 treatment deviation		
Total number of deviations		
Number of treatment deviations per patient		
0		
1		
2		
3		
Type of deviation		
Participant missed a dose of IMP		
Participant received incorrect dose		
Other		

Table 11. Serial haematological and biochemical profiles.

	Before surgery		Day 1 after surgery		Day 2 after surgery		Day 3 after surgery	
	Ivabradine	**Placebo**	**Ivabradine**	**Placebo**	**Ivabradine**	**Placebo**	**Ivabradine**	**Placebo**
Haemoglobin (g/L)								
Creatinine (µmol/L)								
Neutrophil count (10^9L)								
Lymphocyte count (10^9L)								
Albumin (g/L)								

Data reported where available, with (n, %) included for patients with values.

Table 12: Complications

Complication	**Number of patients with available data - no. (%)**		**Summary measure**	
	Ivabradine (n = xxx/XXX)	**Placebo (n = xxx/XXX)**	**Ivabradine**	**Placebo**
Cardiac - no. (%)				
Myocardial infarction				
Arrhythmia				
Cardiogenic pulmonary oedema				
Hypertension				
Bradycardia				
Cardiac arrest with resuscitation				
Respiratory - no. (%)				
Pneumonia				
Pneumothorax				
Bronchospasm				
Aspiration pneumonitis				
Acute lung injury				
Acute respiratory distress syndrome				
Infection - no. (%)				
Surgical site infection (superficial)				
Surgical site infection (deep)				
Surgical site infection (organ space)				
Urinary tract infection				
Infection, source uncertain				
Laboratory confirmed blood stream infection				
Other - no. (%)				
Pulmonary embolism				
Stroke				
Acute psychosis or delirium				

Bowel infarction				
Anastomotic leak				
Perforation of viscus				
Gastro-intestinal bleed				
Other postoperative haemorrhage				
Any other complication				
Acute kidney Injury - no. (%)				

Appendix A: Post Operative Morbidity Survey- POMS

Pulmonary: De novo requirement for supplemental oxygen or other respiratory support (e.g., continuous positive airway pressure or mechanical ventilation)

Infectious: Currently on antibiotics or temperature >38°C in the last 24 hour

Renal: Presence of oliguria (<500 mL/day), increased serum creatinine (>30% from baseline value), or urinary catheter in place for a non-surgical reason

Gastrointestinal: Unable to tolerate an enteral diet (either by mouth or feeding tube) for any reason, including nausea, vomiting and abdominal distension

Cardiovascular: Diagnostic test or therapy in last 24 hours for any of the following reasons: de novo myocardial infarction or ischemia, hypotension (requiring drug therapy or fluid >200 mL/h), atrial or ventricular arrhythmia or pulmonary edema

Neurological: Presence of a de novo focal deficit, coma or confusion/delirium

Wound: Wound dehiscence requiring surgical exploration or drainage or pus from the wound

Haematological: Requirement for any of the following within last 24h: blood, platelets, fresh frozen plasma or cryoprecipitate

Pain: Surgical wound pain significant enough to require parenteral opiates or regional anesthesia.

Appendix B: Pre-defined complications for Clavien-Dindo grading.

Myocardial Infarction: Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of an increase or decrease in cTn values with at least one value above the 99th percentile URL and at least one of the following:

(i) Symptoms of myocardial ischaemia
(ii) New ischaemic ECG changes
(iii) Development of pathological Q waves
(iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
(v) Identification of a coronary thrombus by angiography or autopsy.

Cardiac death Death with a vascular cause and included those deaths after a myocardial infarction, cardiac arrest, and cardiac revascularisation procedure.

Stroke Defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.

Infection Postoperative infection of Clavien-Dindo grade II or greater within 30 days of randomisation, defined as one or more of the following infections, as used in the OPTIMISE-2 trial protocol- full details at https://optimiseii.org/docs/Study%20Protocols/OPTIMISE%20II%20Protocol%20v2.0%2008.12.2020.pdf:

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. Source uncertain; this is defined as an infection which is one or more of the above (i.e. i-vi), but it is unclear which.

Acute heart failure Cardiogenic pulmonary oedema is defined as radiographic or imaging evidence of fluid accumulation in the alveoli due to poor cardiac function, and/or clinical treatment instituted on basis of clinically suspected heart failure.

Respiratory events

Nosocomial pneumonia

Care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia. Nosocomial pneumonia will be characterized as early or late onset i.e. before or after first 4 days of hospitalization. Where repeated episodes of nosocomial pneumonia are suspected, a combination of new signs and symptoms and radiographic evidence or other diagnostic testing will be required to distinguish a new episode from a previous one. This category includes ventilator- associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or endotracheal tube), however care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia.

Nosocomial pneumonia must meet the following criteria:
Two or more serial chest radiographs with at least one of the following: i) New or progressive and persistent infiltrate ii) Consolidation iii) Cavitation

And at least one of the following:
i) Fever (>38°C) with no other recognized cause
ii) Leucopaenia (<4, 000 WBC mm3) or leucocytosis (>12, 000 WBC mm3) iii) For adults >70 years old, altered mental status with no other recognized cause

And at least two of the following:
i) New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements ii) New onset or worsening cough, or dyspnoea, or tachypnoea iii) Rales or bronchial breath sounds iv) Worsening gas exchange
v) Need for invasive or non-invasive mechanical ventilation

Acute kidney injury

A >26ɥmol.L^{-1} increase in serum creatinine or sustained oliguria of <0.5 ml.kg^{-1} hour^{-1} for twelve hours (KDIGO grade 1 or above).

KDIGO staging criteria

KDIGO Staging:

Staging	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥26.5µmol/lincrease	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR<0.3 ml/kg/h for ≥ 24 hours OR Increase in serum creatinine to ≥ 4.0mg/dl (≥353.6 µmol/l) OR Anuria for ≥ 12 hours Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35ml/min per 1.73 m^2	

Infective complications

Infection, source uncertain

Two more of the following associated with strong clinical suspicion of infection (sufficient to require intra-venous antibiotic therapy): i) Core temperature <36ºC or >38ºC ii) White cell count >12 x 109 l-1 or <4 x 109 l-1 iii) Respiratory rate >20 breaths per minute or PaCO2 < 4.5 kPa iv) Pulse rate >90 bpm
v) Radiological investigation for suspected sepsis vi) Specimen/ blood samples sent for microbiological culture.

Urinary tract infection

A symptomatic urinary tract infection must meet at least one of the following criteria:

i) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38oC), urgency, frequency, dysuria, or suprapubic tenderness and patient has a positive urine culture, that is, >105 microorganisms per cm3 of urine with no more than two species of microorganisms. ii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38ºC), urgency, frequency, dysuria, or supra- pubic tenderness and at least one of the following:

a. positive dipstick for leucocyte esterase and/or nitrate;
b. pyuria (urine specimen with >10 WBC mm-3);
c. organisms seen on Gram stain of unspun urine;
d. at least two urine cultures with repeated isolation of the same uropathogen with >102 colonies/mL in non-voided specimens;
e. >105 colonies/mL of a single uropathogen in a patient being treated with an effective antimicrobial agent for a urinary tract infection; f. physician diagnosis of a urinary tract infection;
g. physician institutes appropriate therapy for a urinary tract infection.

Other infections of the urinary tract (kidney, ureter, bladder, urethra, etc.)

Other infections of the urinary tract must meet at least one of the following criteria:

i) Patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site.
ii) Patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation or during a histopathologic examination.
iii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38ºC), localized pain, or localized tenderness at the involved site and at least one of the following:
iv) Purulent drainage from affected site.
v) Organisms cultured from blood that are compatible with suspected site of infection vi) Radiographic evidence of infection, for example, abnormal ultrasound, computed tomography or magnetic resonance imaging; vii) Physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space; viii) Physician institutes appropriate therapy for an infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space.

Surgical site infection SSI (superficial incisional)

A superficial SSI must meet the following criteria:

i) Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following:

a. purulent drainage from the superficial incision.
b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
c. at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
d. diagnosis of superficial incisional SSI by the surgeon or attending physician.

Surgical site infection (deep incisional)

A deep incisional SSI must meet the following criteria:

i) infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following.

ii) Purulent drainage from the deep incision but not from the organ/ space component of the surgical site.

iii) A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC) or localized pain or tenderness, unless incision is culture-negative.

iv) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

v) Diagnosis of a deep incisional SSI by a surgeon or attending physician. An infection that involves both superficial and deep incision sites should be classified as a deep incisional SSI.

Surgical site infection (organ/space)

An organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers that is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection. Listed later are the specific sites that must be used to differentiate organ/space SSI. An example is appendectomy with subsequent sub-diaphragmatic abscess, which would be reported as an organ/space SSI at the intra-abdominal specific site. An organ/space SSI must meet the following criteria: Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and patient has at least one of the following:

i) Purulent drainage from a drain that is placed through a stab wound into the organ/space. ii) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space. iii) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination. iv) Diagnosis of an organ/space SSI by a surgeon or attending physician.

Laboratory - confirmed bloodstream infection

Laboratory - confirmed bloodstream infection must meet at least one of the following criteria:

i) Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.

ii) Patient has a fever (>38oC), chills, or hypotension and at least one of the following:

   a. common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.

   b. common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.

   c. positive antigen test on blood. And signs and symptoms and positive laboratory results are not related to an infection at another site.

Postoperative haemorrhage

Overt blood loss requiring transfusion of two or more units of blood in two hours.

Gastrointestinal bleed
Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz, in practice from the oesophagus, stomach and duodenum.
Lower gastrointestinal bleeding is that originating from the small bowel and colon.

Other postoperative haemorrhage (not gastrointestinal bleed)
Blood loss within 72 hours after the start of surgery, which would normally result in transfusion of blood.

Stroke
Clinical diagnosis with confirmation by CT scan.

Limb or digital ischaemia
Sustained loss of arterial pulse (as determined by palpation or Doppler) or obvious gangrene.

Multi-organ dysfunction syndrome
A life threatening but potentially reversible physiologic derangement involving failure of two or more organ systems not involved in the primary underlying disease process.

Acute psychosis or delirium
Acute episode of severe confusion or personality change, which may result in hallucinations or delusional beliefs in the absence of a pre-existing diagnosis, which may account for the clinical symptoms and signs.

Pulmonary embolism
Computed tomography (CT) pulmonary angiogram with appropriate clinical history.
Acute respiratory distress syndrome According to consensus criteria:
i) Suitable precipitating condition (many causes exist).
ii) Acute onset diffuse bilateral pulmonary infiltrates on chest radiograph.
iii) No evidence of cardiac failure or fluid overload (PAOP < 18 mmHg); iv) Either: PaO_2:FiO2 < 40 kPa = Acute Lung Injury PaO_2:FiO_2 < 27 kPa = Acute Respiratory Distress Syndrome.

Gastro-intestinal bleed
Unambiguous clinical evidence or endoscopy showing blood in gastro-intestinal tract.
Bowel infarction
Demonstrated at laparotomy.

Anastamotic leak
Demonstrated at laparotomy or by contrast enhanced radiograph or CT scan.

Perforated viscus
Clinical diagnosis demonstrated at laparotomy or confirmed by contrast enhanced radiograph or CT scan. For example perforated bowel, gall bladder etc.

Paralytic ileus

Persistent clinical evidence of intestinal ileus and failure to tolerate enteral fluid or feed associated with valid cause.

Appendix C: grading by Clavien-Dindo classification

Grade I: Minor deviations from normal (e.g., a small wound infection).

Grade II: Complications requiring medication or other nonsurgical intervention (e.g., intravenous antibiotics).

Grade IIIa: Complications requiring a non-invasive procedure (e.g., drainage of a haematoma).

Grade IIIb: Complications requiring re-operation or invasive procedures (e.g., surgical repair of a fistula).

Grade IV: Life-threatening complications (e.g., organ failure) requiring intensive care.
and/or also resulting in organ damage.

Grade V: Death resulting from the complication.