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Targeted heart rate control using ivabradine to reduce disease in patients undergoing non-cardiac surgery

Submission date 26/08/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 21/10/2021	**Overall study status** Ongoing	
Last Edited 11/03/2025	**Condition category** Surgery	

Plain English summary of protocol

Background and study aims

Increasingly complex surgical treatments are offered to more patients than ever before. In particular, older patients with serious medical problems are far more likely to undergo surgery today than even 20 years ago. Patients frequently develop medical complications in the days following surgery, including pneumonia and damage to the heart (which is usually undetected by doctors and nurses). Even temporary harm to other parts of the body after surgery prevents individuals from recovering to their normal levels of function. For many patients, this delays further necessary treatments, especially cancer therapies, and increases the risk of dying even after leaving the hospital. The impact of these complications can last months and years, contributing to the increasing number of patients struggling to cope with multiple medical problems (called "multi-morbidity"). Multi-morbidity after surgery is an increasing and unmet healthcare need affecting millions of individuals worldwide each year.

An early feature after surgery in many patients is damage to the heart, which reflects cell damage that is happening at the same time to many other parts of the body. Problems with a specialised nerve called the vagus nerve which helps control the speed at which the heart beats, are often linked to heart damage and other complications after surgery. Poor vagus nerve activity causes a higher heart rate, which is strongly linked to heart damage and coincides with other organs of the body not working normally. Our aim is to protect both the heart and other body organs by lowering heart rate after surgery, to ensure that patients gain the best possible result from surgery with rapid recovery and as few complications as possible. In this trial, ivabradine will be used to slow heart rate with minimal effects on other functions including blood pressure.

FUNNY is a clinical trial to establish whether the targeted lowering of heart rate is beneficial for patients aged 55 years and over undergoing elective or urgent non-cardiac surgery. 350 patients will be enrolled over a three-year recruitment window across all hospitals. We aim to address the following research question does slowing the speed of the heart beating reduce damage caused to the heart after surgery? We will also look into the number of harmful events including postoperative infections, kidney damage and respiratory complications within 30 days of surgery.

Who can participate?
Adults aged 55 years and over who are undergoing elective or urgent non-cardiac surgery requiring general and/or regional anaesthesia with sedation, expected to take longer than 120 minutes from the induction of anaesthesia, with at least one medical risk factor for perioperative myocardial injury and history of hypertension or hypertension recorded at the pre-assessment clinic.

What does the study involve?
Before surgery, participants are randomly allocated to either receive ivabradine or placebo. The study is blinded so the trial participants, healthcare staff, local investigators collecting outcome data, and investigators at the central coordinating centre will not know which treatment the patients are receiving. The treatment will be administered twice a day with a 12 hour (± 2 hours) gap in-between the administrations starting on the day of surgery before the induction of anaesthesia and continue on postoperative day one and day two. The treatment will last for a maximum of three days or less if the patient in discharged. The number of tablets per dose is dependent on the heart rate recorded within one hour before dosing. To assess whether the patient's heart shows any signs of stress, additional blood samples will be collected on the following time points: preoperatively before induction of anaesthesia on the day of surgery, on postoperative day one, postoperative day two and postoperative day three provided the patient has not been discharged earlier than these timepoints. At selected centres, heart rate will be measured using a Holter and blood pressure using an ambulatory blood pressure monitor cuff. The patient will wear these monitors for at least one hour before induction of anaesthesia until postoperative day three or discharge (whichever is earlier).

At postoperative day one, intraoperative information, administration of drug and safety events will be measured. Similar assessments will be made on day two and day three postoperatively. On hospital discharge, there will be a review of the medical notes for complications and adverse events will be assessed. 30 days after surgery, the research team will review the patient's medical record to assess specific postoperative complications and any treatments received as a result. The research team will contact the patient to conduct a brief telephone interview on their recovery. At 180 days after surgery the mortality status of the patient will be confirmed by reviewing their hospital records.

What are the possible benefits and risks of participating?
There are no guaranteed benefits to the trial participants however the study might benefit patients undergoing surgery in the future. Ivabradine is a licensed drug commonly used to treat chronic heart failure and the symptoms of chronic angina. It is generally safe and most people do not have any problems. But like all medicines, it can cause side effects in some people. The side effects of ivabradine include:
• Very common (may affect more than 1 in 10 people): Luminous visual phenomena (brief moments of increased brightness, most often caused by sudden changes in light intensity). They can also be described as a halo, coloured flashes, image decomposition or multiple images. They generally occur within the first two months of treatment after which they may occur repeatedly and resolve during or after treatment.
• Common (may affect up to 1 in 10 people): Modification in the heart functioning (the symptoms are a slowing down of the heart rate). They particularly occur within the first 2 to 3 months of treatment initiation. Other common side effects include headache, dizziness, blurred vision (cloudy vision), irregular rapid contraction of the heart, abnormal perception of heartbeat and uncontrolled blood pressure.
• Uncommon (may affect up to 1 in 100 people): Fainting, double vision, impaired vision, spinning sensation (vertigo), palpitations and cardiac extra beats, low blood pressure, difficulty breathing

(dyspnoea), feeling sick (nausea), constipation, diarrhoea, abdominal pain, skin rash, muscle spasms, feeling of tiredness, feeling of weakness, swollen face, tongue or throat, difficulty in breathing or swallowing (angioedema), changes in laboratory parameters: an excess of eosinophils (a type of white blood cell), high blood levels of uric acid, elevated creatinine in blood (a breakdown product of muscle), abnormal ECG heart tracing.
• Rare (may affect up to 1 in 1,000 people): Skin reddening, itching, urticaria, feeling unwell.
• Very rare (may affect up to 1 in 10,000 people): Irregular heartbeats.

Where is the study run from?
Critical Care and Perioperative Medicine Research Group (CCPMG) at the Royal London Hospital (UK).

When is the study starting and how long is it expected to run for?
February 2021 to March 2026

Who is funding the study?
National Institute for Health Research (NIHR) (UK).

Who is the main contact?
1. Ms Tasnin Shahid (public), t.shahid@qmul.ac.uk
2. Dr Priyanthi Dias (scientific), p.dias@qmul.ac.uk

Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-002099-11

Integrated Research Application System (IRAS)
1003561

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
012663, IRAS 1003561

Study information

Scientific 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 randomised trial

Acronym
FUNNY

Study objectives
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.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/05/2021, London Westminster Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 1048012; westminster.rec@hra.nhs.uk), ref: 21/LO/0069

Study design
Phase IIa triple blind placebo controlled randomized trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Patients undergoing elective or urgent non-cardiac surgery requiring general and/or regional anaesthesia with sedation

Interventions
Following provision of informed consent, participants will be centrally allocated to one of two 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) and (2) trial centre.

The trial intervention will start on the day of surgery before the induction of anaesthesia and continue on postoperative day one and day two (unless MAP is <60 or new onset arrhythmia). Patients will receive either ivabradine or placebo twice daily from the allocated IMP kit with a 12-hour (± 2 hours) gap in-between the administrations.
Treatment breaks are not permitted. The number of tablets per dose is dependent on the heart rate recorded within one hour before dosing. If no measurements are available, heart rate will be measured before drug administration. If multiple measurements have been recorded within one hour before dosing, the lowest value will be taken to consider the dose of IMP. The tablets should be administered orally by a medically qualified person and documented in the medical notes. Treatment will continue for a maximum of three days, or less if the patient is discharged. Tablets will be crushed for delivery via nasogastric (NG) tube on the few occasions when patient may be unable to swallow after surgery (e.g., after some gastrointestinal surgery).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
ivabradine

Primary outcome(s)
The primary outcome is a composite of myocardial injury associated with morbidity within seven days of surgery. To meet the criteria for the primary outcome, the patient must experience the following:
1. Increase in serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) concentration (measured using blood test) of:
a. An absolute value of ≥15ng/L-1 on day one, day two or day three after surgery, OR
b. An increase of ≥5 ng/L-1 from the preoperative value on day one, day two or day three after surgery when the preoperative value was ≥15ng/L-1, AND
2. Any POMS defined morbidity domain on day three or day seven after surgery measured from patient records

Key secondary outcome(s))
1. Any POMS defined morbidity domain on day three or seven after surgery measured from patient records
2. Levels of serum high-sensitivity troponin-T (Elecsys, Roche Diagnostics) measured using blood

test on day one, day two and day three after surgery
3. Predefined complications at day 30 after surgery graded using the Clavien-Dindo classification measured from patient records

Completion date
31/03/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria of as 07/03/2023:
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 the induction of anaesthesia
3. At least one medical risk factor for perioperative myocardial injury
4. History of hypertension (requiring anti-hypertensive drug) or hypertension recorded in the pre-assessment clinic [BP>140mmHg systolic; >90 mmHg diastolic]

Previous participant 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 the induction of anaesthesia
3. At least one medical risk factor for perioperative myocardial injury

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
55 years

Sex
All

Total final enrolment
350

Key exclusion criteria
Current participant exclusion criteria of as 07/03/2023:
1. Inability or refusal to provide informed consent
2. Patients lacking capacity
3. Prior use of ivabradine within the previous 30 days
4. Current participation in a clinical trial of a treatment with a similar biological mechanism

5. Previous enrolment into FUNNY trial
6. Contraindication to ivabradine
7. History of hypersensitivity or allergy to ivabradine or any of its excipients
8. Women of childbearing potential (this includes pregnancy and lactation). A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant unless permanently sterile
9. Patients with atrial fibrillation (persistent/chronic or paroxysmal)

Previous participant exclusion criteria:
1. Inability or refusal to provide informed consent
2. Patients lacking capacity
3. Prior use of ivabradine within the previous 30 days
4. Current participation in a clinical trial of a treatment with a similar biological mechanism
5. Previous enrolment into FUNNY trial
6. Contraindication to ivabradine
7. History of hypersensitivity or allergy to ivabradine or any of its excipients
8. Women of childbearing potential (this includes pregnancy and lactation). A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant unless permanently sterile

Date of first enrolment
21/12/2021

Date of final enrolment
06/03/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal London Hospital
Whitechapel Road
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Study participating centre
Newham University Hospital
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Study participating centre
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Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and analysed during the current study will be available upon request. Ideally, the Chief Investigator (CI), Professor Gareth Ackland should be contacted first with the enquiry at admin@funnytrial.org for CI approval. Data would typically only be available to share at the end of the study.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		19/02/2025	11/03/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes