

BMJ Open Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) trial: study protocol for a multicentre international trial of cardiac output-guided fluid therapy with low-dose inotrope infusion compared with usual care in patients undergoing major elective gastrointestinal surgery

To cite: Edwards MR, Forbes G, MacDonald N, *et al.* Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) trial: study protocol for a multicentre international trial of cardiac output-guided fluid therapy with low-dose inotrope infusion compared with usual care in patients undergoing major elective gastrointestinal surgery. *BMJ Open* 2019;**9**:e023455. doi:10.1136/bmjopen-2018-023455

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-023455>).

Received 6 April 2018

Revised 1 August 2018

Accepted 10 October 2018



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ABSTRACT

Introduction Postoperative morbidity and mortality in older patients with comorbidities undergoing gastrointestinal surgery are a major burden on healthcare systems. Infections after surgery are common in such patients, prolonging hospitalisation and reducing postoperative short-term and long-term survival. Optimal management of perioperative intravenous fluids and inotropic drugs may reduce infection rates and improve outcomes from surgery. Previous small trials of cardiac-output-guided haemodynamic therapy algorithms suggested a modest reduction in postoperative morbidity. A large definitive trial is needed to confirm or refute this and inform widespread clinical practice.

Methods The Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) trial is a multicentre, international, parallel group, open, randomised controlled trial. 2502 high-risk patients undergoing major elective gastrointestinal surgery will be randomly allocated in a 1:1 ratio using minimisation to minimally invasive cardiac output monitoring to guide protocolised administration of intravenous fluid combined with low-dose inotrope infusion, or usual care. The trial intervention will be carried out during and for 4 hours after surgery. The primary outcome is postoperative infection of Clavien-Dindo grade II or higher within 30 days of randomisation. Participants and those delivering the intervention will not be blinded to treatment allocation; however, outcome assessors will be blinded when feasible. Participant recruitment started in

Strengths and limitations of this study

- This will be the largest contemporary randomised trial examining the effectiveness and safety of perioperative cardiac output-guided haemodynamic therapy in patients undergoing major elective gastrointestinal surgery.
- The primary outcome is postoperative infection, which is a major healthcare burden of clear importance to patients.
- The multicentre, international design and broad inclusion criteria support the external validity of the trial.
- Although the clinical teams delivering the trial interventions will not be blinded, research staff assessing clinical outcomes will not be aware of treatment group allocation.

January 2017 and is scheduled to last 3 years, within 50 hospitals worldwide.

Ethics/dissemination The OPTIMISE II trial has been approved by the UK National Research Ethics Service and has been approved by responsible ethics committees in all participating countries. The findings will be disseminated through publication in a widely accessible peer-reviewed scientific journal.

Trial registration number ISRCTN39653756.

INTRODUCTION

Surgery is an increasingly popular treatment, with an estimated 310 million operations carried out each year worldwide.^{1 2} Although serious failures in surgical or anaesthetic technique are rare, complications during recovery from surgery are much more common. Older patients with comorbidities undergoing major gastrointestinal surgery are at particularly high risk of postoperative morbidity.^{3–5} Hospital-acquired infections occur frequently in this group because of the physiological and inflammatory changes caused by the tissue injury of major surgery, combined with bacterial microexposure due to surgical manipulation of the gut. Meanwhile, the consequences of infection are more serious because of the reduced physiological reserve in this patient group.^{2–7}

In the UK alone, >50 000 patients aged ≥ 65 years undergo major elective gastrointestinal surgery each year.⁸ One-third of these patients will develop a hospital-acquired infection, including surgical-site infections, body cavity infections and pneumonia. These infections cause prolonged hospitalisation, increased healthcare costs, reduced short-term and long-term quality of life and premature death.⁶ Around 10% of this patient group dies within 6 months of surgery.⁹

Cardiac output monitoring to guide intravenous fluid and inotropic drugs as part of a haemodynamic therapy algorithm may reduce postoperative infections by improving tissue perfusion and oxygenation, and modifying inflammatory pathways.^{10–12} There is some evidence that this treatment may also reduce the incidence of acute kidney injury, another important complication which occurs more frequently after major gastrointestinal surgery.¹³

Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) was the largest contemporary trial of this intervention in 734 high-risk patients undergoing gastrointestinal surgery.^{9 14} The use of a cardiac output-guided haemodynamic therapy algorithm did not reduce a composite outcome of complications and 30-day mortality compared with usual care. However, inclusion in an updated meta-analysis indicated that the intervention was associated with a reduction in complication rates (intervention, 488/1548 (31.5%) vs control, 614/1476 (41.6%); RR, 0.77 (95% CI 0.71 to 0.83)). The intervention was associated with a reduced incidence of postoperative infection (intervention, 182/836 (21.8%) vs control, 201/790 (25.4%); RR, 0.81 (95% CI 0.69 to 0.95)) and a reduced duration of hospital stay (mean reduction, 0.79 days (95% CI 0.62 to 0.96)). Mortality at longest follow-up showed a non-significant reduction following the intervention (intervention, 267/3215 deaths (8.3%) vs control, 327/3160 deaths (10.3%); RR 0.86 (95% CI 0.74 to 1.00)). Five participants in the OPTIMISE intervention group had a serious adverse cardiac event within 24 hours of surgery compared with none in the control group. However, this was not a significant difference, and postoperative troponin levels were similar in both trial groups.¹⁵

These findings suggest, but do not confirm, that perioperative cardiac output-guided haemodynamic therapy reduces postoperative infections and other complications.¹⁶ In the absence of conclusive data, this technology has only been partially adopted into routine practice because of doubts within the clinical community regarding the evidence base.^{17 18} A definitive trial is needed to confirm the effectiveness and cardiac safety of this intervention and inform routine clinical practice for a large number of patients worldwide.

Study hypotheses

We hypothesise that in high-risk patients undergoing major elective gastrointestinal surgery cardiac output-guided fluid therapy combined with low-dose inotrope infusion reduces the incidence of postoperative infections within 30 days of randomisation compared with usual care. Secondary hypotheses are that this intervention reduces acute kidney injury within 30 days of randomisation, reduces mortality within 180 days, is cost effective and does not lead to an excess of postoperative adverse cardiac events.

METHODS AND ANALYSES

The protocol was developed in line with Standard Protocol Items for Randomized Trials recommendations.¹⁹

Study design

Multicentre, international, open, two-arm, parallel group randomised controlled trial.

Setting

Surgical services of 50 hospitals worldwide. Participant recruitment started in January 2017 and is scheduled to last 3 years. Recruiting site eligibility criteria include having surgical services performing major elective gastrointestinal surgery in adults, the ability to provide cardiac output monitored haemodynamic therapy and previous participation in interventional research.

Participants

Inclusion criteria

Patients aged ≥ 65 years, with an American Society of Anesthesiologists (ASA) physical status classification of II or greater, undergoing major elective surgery involving the gastrointestinal tract that is expected to take longer than 90 min.

Exclusion criteria

Patient refusal of informed consent, clinician refusal, patients expected to die within 30 days, acute myocardial ischaemia or acute pulmonary oedema in the previous 30 days, any contraindication to low-dose inotropic medication, pregnancy, previous enrolment in the OPTIMISE II trial or current participation in another clinical trial of a treatment with a similar biological mechanism or primary outcome measure. Patients undergoing procedures

involving only the liver, gallbladder or pancreas but without resection of bowel are not eligible for inclusion.

Enrolment and randomisation

Strategies for achieving adequate participant enrolment will include ensuring the target number of suitable recruiting sites is achieved, coordinated trial leadership at an international, national and hospital level, local engagement of surgeons, anaesthetists and intensivists to support screening and trial delivery, and selecting sites with experienced local investigators and research teams. A full list of OPTIMISE II investigators is included in online supplementary file 1. Public and patient input to the trial design has informed the trial participant experience and consent materials to ensure they are acceptable. Recruitment targets will be monitored, fed back to sites and actively managed throughout the trial.

Potential participants will be screened by research staff at the site having been identified from pre-admission clinic lists, operating theatre lists and by communication with nursing and medical staff. Before surgery, potential participants will be identified and approached by a member of the research team. Wherever possible, the patient will be approached at least 24 hours prior to surgery although due to the nature of the trial inclusion criteria, shorter time frames are permitted.

Written informed consent will be obtained from each subject prior to participation in this trial. This process will include provision of a patient information sheet (see online supplementary file 2) accompanied by the relevant consent form (see online supplementary file 3), and an explanation of the aims, methods, anticipated benefits and potential harms of the trial. Patients who lack capacity to give or withhold informed consent will not be recruited. Eligible patients who are not entered into this trial will be recorded (including reason not entered).

Randomisation will occur after the participant has provided informed consent and shortly before the surgical procedure is due to start. Participants will be randomised in a 1:1 ratio by minimisation with a random component, with group allocation carried out using a central online service. Minimisation variables will be country, surgical procedure category and ASA class. The surgical procedure categories are resection of colon, rectum or small bowel; resection of pancreas and bowel; resection of stomach (non-obesity surgery); resection of oesophagus (non-obesity surgery); obesity surgery and other surgery involving gut resection. The ASA classes are II, III and IV. Each participant will be allocated with 80% probability to the group that minimises the between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. A participant's treatment group allocation will only be revealed once the randomisation is complete.

Perioperative management

The trial intervention period will commence at the start of general anaesthesia and continue until 4 hours after

the completion of surgery (maximum total duration: 24 hours). Care for all participants has been loosely defined to avoid extremes of clinical practice but also practice misalignment.²⁰ All participants will receive standard measures to maintain oxygenation ($\text{SpO}_2 \geq 94\%$), haemoglobin ($>8\text{g/L}$), core temperature (37°C) and heart rate ($<100\text{bpm}$). A fluid selected by clinicians will be administered at 1mL/kg/hour to satisfy maintenance fluid requirements; 5% dextrose is recommended. Additional fluid will be administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. For fluid boluses clinicians may choose from 'balanced' crystalloids, 0.9% sodium chloride, gelatin-based or starch-based colloids or albumin. Mean arterial pressure will be maintained between 60 and 100 mm Hg using an alpha adrenoceptor agonist or vasodilator as required. Postoperative analgesia will be provided at the discretion of the clinician in accordance with local protocols. This may include epidural infusion (bupivacaine and fentanyl), intrathecal opioids (fentanyl, morphine, diamorphine), wound catheter infusion (bupivacaine), opioid-based patient-controlled analgesia system, oral analgesics (including opioids) or intravenous infusion (opioids or lidocaine). If required, postoperative sedation will be provided with propofol or midazolam.

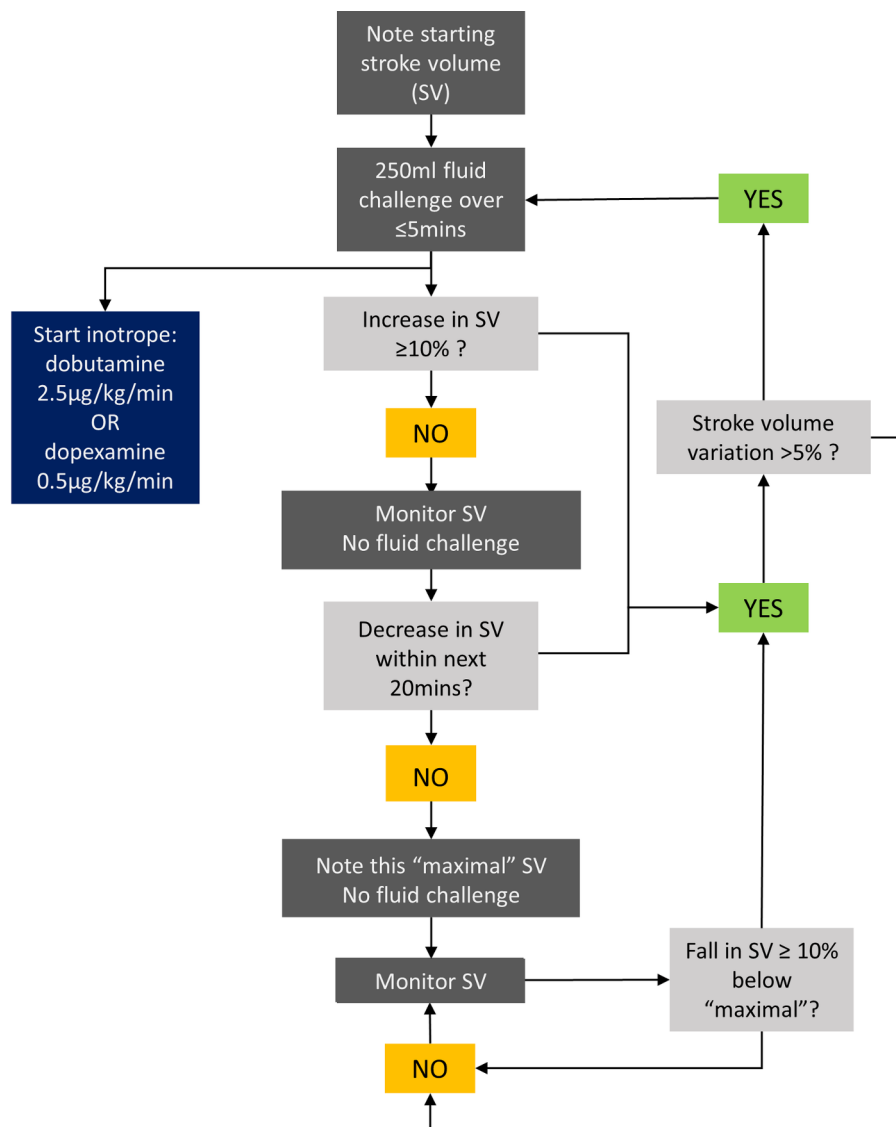
Study interventions

Control group

Participants in the control group will be managed by clinical staff according to usual practice. This will include 250 mL fluid challenges as above administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. If a specific haemodynamic end point for fluid challenges is to be used, the most appropriate would usually be a sustained rise in central venous pressure of at least 2 mm Hg for 20 min or more. Patients should not be randomised if the clinician intends to use cardiac output monitoring regardless of study group allocation; this is considered 'clinician refusal' and is a specific exclusion criterion. However, clinical staff are free to request cardiac output monitoring if this is required to inform the treatment of a participant who becomes critically ill (eg, because of severe haemorrhage) during the trial intervention period. These events will be recorded as protocol deviations.

Intervention group

The intervention will commence from the induction of general anaesthesia and continue for 4 hours following surgery. Cardiac output, stroke volume and stroke volume variation (SVV) will be measured by cardiac output monitor. Investigators may only use commercially available cardiac output monitoring equipment provided by Edwards Lifesciences (Irvine, California, USA) in this trial. The system comprises an EV1000 monitor and ClearSight (non-invasive) or FloTrac



General haemodynamic measures (all patients)

1. Maintenance fluid at 1ml/kg/hr - dextrose 5% recommended
2. Transfuse blood to maintain haemoglobin >80 g/l
3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload
4. Mean arterial pressure 60-100 mmHg; SpO₂ ≥94%; temperature 37°C; heart rate <100 bpm

Figure 1 Algorithm for cardiac output-guided haemodynamic therapy for participants in the Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II intervention group.

(invasive arterial pressure) sensor. Clinicians will be able to choose between the two sensors on a participant-by-participant basis. No more than 500 mL of intravenous fluid will be administered prior to commencing cardiac output monitoring. In addition to the maintenance, fluid participants will receive 250 mL fluid challenges with a recommended solution as required in order to achieve a maximal value of stroke volume (see figure 1). The absence of fluid responsiveness will

be defined as the absence of a sustained rise in stroke volume of at least 10% for ≥20 min. A low SVV value also indicates a low probability of fluid responsiveness²¹ so a fluid bolus should not be given if the SVV is <5%. In addition, participants will receive a low-dose inotrope infusion at a fixed rate that will be commenced after fluid replacement has been initiated. The choice of inotrope will be made at the discretion of the local investigator, according to local preference and availability.

The options are dobutamine at a dose/rate of 2.5 µg/kg/min and dopexamine at an equipotent dose/rate of 0.5 µg/kg/min. The infusion rate will be reduced and/or discontinued if the participant develops a tachycardia (heart rate >100 bpm) for >30 min despite adequate anaesthesia and analgesia. Data collection and follow-up for such participants will be performed as normal. All other management decisions will be taken by clinical staff.

Blinding and procedures to minimise bias

OPTIMISE II is a pragmatic trial of a treatment algorithm. It is not possible to conceal treatment allocation from all staff in trials of this type. Therefore, this trial will be open-label, and participants and the staff delivering the intervention will be unblinded. However, procedures will be put in place to minimise the possibility of bias arising because research staff become aware of treatment group allocation. Those assessing clinical outcomes (research associates and principal investigators (PIs)) should not be involved in the participant's care and should be unaware of treatment group allocation. Those contacting the participant during follow-up (eg, at day 30) should also be unaware of treatment group allocation. The research associate undertaking the participant follow-up will make a self-assessment of their degree of blinding after the visit.

The randomisation method used is not predictable so there is little risk of selection bias for research staff enrolling patients.²² The trial management group and the trial steering committee will not see results broken down by treatment arm during the trial. Final analysis will occur once all follow-up data are collected, the final statistical analysis plan has been signed off and data cleaning has occurred. The independent data monitoring committee will see outcome results by treatment group but data will be handled by an independent statistician, not otherwise involved in the trial.

Data collection

Postoperative outcomes will be recorded by research staff that are unaware of study group allocation as detailed below and entered onto paper case report forms before entry onto the secure web-based data entry platform. A full list of data collected from all participants is included in online supplementary file 1. Data will be collected from all participants randomised regardless of whether the participant received the intervention according to the trial protocol or not. The occurrence of a specified clinical outcome will be confirmed by the local PI, or an appropriately qualified delegate if the PI is aware of the participant group allocation.

Data monitoring

The sponsor will have oversight of trial conduct at sites, with the Trial Management Group having day-to-day responsibility for quality control and quality assurance of the data collected. An independent Data Monitoring and Ethics Committee (DMEC) and a Trial Steering

Committee (TSC) have been appointed and function in accordance with an agreed charter. DMEC and TSC reviews will be held sixmonthly, or less frequently if deemed appropriate by the respective committees. No formal interim analysis for efficacy is planned. However, the DMEC will monitor the safety and efficacy of the interventions during the period of recruitment into the trial. The DMEC will review patient recruitment, data quality, protocol compliance and loss to follow-up. The DMEC will make recommendations to the TSC who will make final decisions on trial continuation.

Trial outcomes

Primary end point

The primary end point of the trial is postoperative infection rate within 30 days of randomisation. This is defined as one or more of the following infections of Clavien-Dindo grade II or greater: superficial surgical site infection, deep surgical-site infection, organ space surgical-site infection, pneumonia, urinary tract infection, laboratory-confirmed blood stream infection or infection, source uncertain; this is defined as an infection which could be more than one of the above but it is unclear which.

Secondary end points

1. Mortality within 180 days of randomisation.
2. Acute kidney injury of Clavien-Dindo grade II or greater within 30 days from randomisation.
3. Acute cardiac event of Clavien-Dindo grade II or greater within 24 hours of randomisation. This is defined as one or more of arrhythmia, myocardial infarction, myocardial injury after non-cardiac surgery, cardiac arrest with successful resuscitation or cardiogenic pulmonary oedema.
4. Acute cardiac event of Clavien-Dindo grade II or greater within 30 days of randomisation.

Planned process measures

1. Duration of hospital stay (number of days from randomisation until hospital discharge).
2. Number of critical care free days, up to 30 days from randomisation. A critical care free day is defined as a day in which the participant is alive and is not in a level 2 or level 3 critical care bed.

Health economic outcomes

1. Healthcare costs during 180 days from randomisation from the perspective of UK health services.
2. Quality-adjusted life-years (QALYs) during 180 days from randomisation.
3. Incremental cost-effectiveness ratio.

Assessment of outcomes

The primary outcome will be assessed using information from a participant's medical records. Participants discharged from hospital before day 30 will be contacted shortly after day 30 to ascertain whether they have received any new treatment since discharge, or if they have been readmitted to hospital or seen a doctor since discharge.

allow us to detect an absolute reduction in the primary outcome of 6% (from 30% to 24%) with 92% power.

Statistical analysis

Analyses will be performed according to intention-to-treat; all participants with a recorded outcome will be included in the analysis, and analysed according to the treatment to which they were randomised.²³ Summary statistics by group, treatment effects, 95% CIs and p values will be presented for primary and secondary outcomes, and process measures. Baseline and all other follow-up data for the two groups will be summarised by treatment group, but not subjected to statistical testing.

The primary outcome of postoperative infection within 30 days from randomisation will be analysed using a mixed-effects logistic regression model with a random intercept for country.²⁴ The model will adjust for surgical procedure category, age, gender, ASA class, baseline haemoglobin and baseline creatinine. ASA class and procedure category will be included as categorical variables. The categories for ASA class are II, III and IV. The categories for procedure are (1) resection of colon, rectum or small bowel; (2) resection of pancreas and bowel; (3) resection of stomach (non-obesity surgery); (4) resection of oesophagus (non-obesity surgery); (5) obesity surgery; and (6) other surgery involving gut resection. Age, baseline haemoglobin and baseline creatinine will be adjusted for using restricted cubic splines with three knots, and knot locations based on Harell's recommendations.^{25 26} Missing baseline data will be accounted for using mean imputation.²⁷ P values <0.05 will be considered statistically significant. A statistical analysis plan will be signed off prior to (1) data analysis taking place and (2) any member of the trial team having access to unblinded data.

Subgroup analysis

A subgroup analysis will be performed for the primary outcome (postoperative infection within 30 days of randomisation) to assess whether the effect of the intervention differs by planned surgical procedure category. Planned surgical procedure category has six categories: (1) resection of colon, rectum or small bowel; (2) resection of pancreas and bowel; (3) resection of stomach (non-obesity surgery); (4) resection of oesophagus (non-obesity surgery); (5) obesity surgery and (6) other surgery involving gut resection.

Health economic analysis

A cost-utility analysis will evaluate the cost-effectiveness of cardiac output-guided fluid therapy with low-dose inotrope infusion compared with current usual practice from the perspective of the UK health services. Costs and outcomes will be evaluated over 180 days of follow-up from randomisation. The analysis will include the cost of intervention and the cost of hospital care incurred by patients during this 180-day period. The resources incurred for cardiac output monitoring in the intervention arm will be

obtained from trial centres. Data on hospital admissions will be recorded on the Case Report Form. For UK participants, secondary care electronic health records over the trial duration period will be obtained from NHS Digital Hospital Episode Statistics.²⁸ Data on hospital admissions, critical care and outpatient visits will be combined with published unit costs to estimate the respective hospital care costs.²⁹

Outcomes in the health economic analysis will be measured in terms of QALY estimated using the EQ-5D-3L questionnaire data, collected at baseline, 30 and 180 days for UK participants, and UK population utility weights.³⁰ Appropriate statistical techniques will be applied to evaluate cost-effectiveness of cardiac output-guided fluid therapy with low-dose inotrope infusion using the trial-wide data and the more detailed further data collected for UK participants. The analysis will gauge the additional cost per QALY gained in the intervention arm compared with usual care using an incremental cost-effectiveness ratio (ICER). Non-parametric bootstrapping with replacement using 5000 iterations based on the observed data will be carried out to estimate the 95% CI for the ICER and summarise the probability of the intervention to be cost-effectiveness across a range of cost-effectiveness thresholds.³¹

Safety monitoring

All interventions within the OPTIMISE II trial are already in routine clinical use for patients undergoing major gastrointestinal surgery. The safety of the intervention will be monitored by recording acute cardiac events at 24 hours and 30 days after randomisation as a trial outcome. These events will be monitored at intervals by the DMEC and will not be recorded separately as an adverse event. Serious adverse events (SAEs) will be reported to the trial sponsor within 72 hours of research sites becoming aware of them. An SAE is defined as an adverse event resulting in death, threat to life, hospitalisation (or prolongation of hospitalisation) or persistent disability/incapacity which is judged to be related to the use of study procedures, and not an expected occurrence after abdominal surgery.

Monitoring/auditing

The trial will be audited annually by the sponsor trials unit. In addition, each recruiting site will have two on-site monitoring visits during the trial recruitment period. If required, additional monitoring visits may be organised to address specific trial related problems at a site. Full source data verification will be carried out for the primary outcome at 30-day follow-up for up to 10 patients at each site visit.

Patient and public involvement

The OPTIMISE II trial was reviewed in detail by the Royal College of Anaesthetists Patient, Carer and Public Involvement and Engagement (PCPIE) in Research Group which was formed to provide high-quality guidance on research

proposals in the field of perioperative medicine. Detailed feedback from this group has informed both the design and conduct of the trial. The group agreed that the findings of the previous smaller trial (OPTIMISE) were not conclusive and required confirmation. Importantly, the recently completed James Lind Alliance Priority Setting Partnership for Anaesthesia and Perioperative Care has ranked this topic among the 10 most important research questions in our field. This confirms the importance of this research question to both patients and clinicians. The RCoA PCPIE group nominated a member to join the OPTIMISE II project group as a lay representative. This member has been involved throughout the preparation of the trial, providing detailed input and representing the views of the PCPIE group with respect to issues of safety and the experience of participating patients. The Trial Steering Committee includes a lay member, providing independent non-medical input to trial conduct. A lay summary of the trial results will be made available to participants.

Ethics and dissemination

The OPTIMISE II trial has been approved by the UK National Research Ethics Service and has been approved by responsible ethics committees in all participating countries. All participating centres have full ethical approval. Any additional recruiting sites joining the trial will require full ethical approval prior to participation. 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 OPTIMISE II Trial Group. Further dissemination will include presentations at international scientific meetings, public presentations, webcasts and reports targeting international healthcare policymakers, professional organisations, front-line healthcare workers, patients and the public. Deidentified data will also be shared with other authenticated researchers for further research and research publications on this topic, but only if they guarantee to preserve the confidentiality of the information requested. Requests for data sharing will be considered by the data sharing committee of the supporting trials unit (Pragmatic Clinical Trials Unit, Queen Mary University of London) in accordance with their data sharing policy.

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Acknowledgements The Royal College of Anaesthetists Health Services Research Centre PCPIE group, Lauren Osborne and Sara Payne have provided lay input to trial design and conduct.

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Suarez; Cano Peral; Rafael Uña-Orejón; María V. Caldera-Álvarez; Silvia Fernández-Francos; Azahara Sancho Dávila; Carlos Ferrando Ortolá; Andrea Gutierrez; Ana Mugarra; Esther Romero; Marina Soro; Estefanía Gracia; Natividad Pozo; Ana Perez Villafañe; Ana Fernandez Diez; Cristina García Miguel Sánchez; Fernando Díez Búrón; Rodrigo Pérez Blanco; Marina Varela Duran; Pilar Díaz Parada; Marina Barreiro Torres; Marta Casalderey Rivas; Susana Marcelo Brage; Ana María González Castro; María José Pampín Conde; Cristina Barreiro Pardal; María Rosa Taboada Ben; Ana Pérez; Jaime Miralles Sancho; María Mercader Alarcón; Christoph Hofer; Sergio Mariotti; Isabel Marcolino; Andreas Winter; Tracy McGrane; Debra Craven; Teresa Turnbo; Gail Mayo; Derwin Campbell; Steven Klintworth; Amanda Tilley; Mitchell Weinstein; Annamarie Horan; Rupa Chowdary; Vittoria Arslan Carlon; Tasneem Balasinorwala; Gloria Yang.

Contributors RMP contributed to the conception of the study. MRE, RMP, GF, BCK, MPWG, MGM, VB and BM contributed to the design of the study. MRE wrote the first draft of the protocol. MRE, RMP, GF, BCK, NM, MPWG, MGM, VB, BM, PD, AT, MAG, MS, TDP, LE, DNW, SAM, CA, JR-M, CKH, HA, WS, LH and IG revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published. All OPTIMISE II Investigators have implemented and are conducting the trial in their local research site.

Funding The OPTIMISE II trial is supported by Edwards Lifesciences (Irvine, CA) and the UK National Institute for Health Research through RMP's NIHR Professorship.

Competing interests MRE has received an honorarium for lecturing for Edwards Lifesciences and is Chief Investigator of the NIHR-funded FLO-ELA trial of cardiac output-guided haemodynamic therapy in patients undergoing emergency abdominal surgery. MPWG reports serving as Medical Advisory Board, Sphere Medical Ltd; Director, EBPO Social Enterprise; Director, Oxygen Control Systems Ltd; Director, EBPO USA. UK NIHR CRN National Specialty Lead for Anaesthesia, Perioperative Medicine and Pain. Joint Editor-in-Chief, Perioperative Medicine. MGM reports personal fees from Deltex Medical, personal fees from Edwards Lifesciences, personal fees from Baxter, grants from Smiths Medical, outside the submitted work. In addition, MGM has a patent 'QUENCH' (clinical hydration solutions limited) a patient hydration device (issued). MS reports grants from Edwards Lifesciences, during the conduct of the study; grants from Medtronic, grants from AMOMED, grants from Edwards Lifesciences, grants from Gettinge Group, outside the submitted work. TDP reports grants from Australian and New Zealand College of Anaesthetists, during the conduct of the study. LE reports personal fees from Cogstate, outside the submitted work. DAM reports personal fees from Edwards Lifesciences, outside the submitted work. JR-M reports personal fees from Edwards Lifesciences, during the conduct of the study; personal fees and non-financial support from Edwards Lifesciences, from Fresenius Kabi, from Deltex Medical, outside the submitted work. RMP holds research grants, and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Medtronic, Glaxo Smithkline, Intersurgical, and Edwards Lifesciences, and is a member of the Associate editorial board of the British Journal of Anaesthesia. RMP is supported in part by an NIHR Professorship. The OPTIMISE II trial is adopted by the UK Perioperative Medicine Clinical Trials Network. DNW is supported in part by a New Investigator Award from the Canadian Institutes of Health Research and a Merit Award from the Department of Anesthesia at the University of Toronto.

Patient consent for publication Not required.

Ethics approval The OPTIMISE II trial has been approved by the UK National Research Ethics Service (London, Brent Research Ethics Committee, ref 16/LO/2067; IRAS 209688) and has been approved by responsible ethics committees in all participating countries.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Deidentified data will be shared with other authenticated researchers for further research and research publications on this topic, but only if they guarantee to preserve the confidentiality of the information requested. Requests for data sharing will be considered by the data sharing committee of the supporting trials unit (Pragmatic Clinical Trials Unit, Queen Mary University of London) in accordance with their data sharing policy.

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