Cardiac output-guided haemodynamic therapy for patients undergoing major gastrointestinal surgery: OPTIMISE II randomised clinical trial

OPTIMISE II Trial Group

Correspondence to: M Edwards
Department of Anaesthesia, Southampton General Hospital, University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, UK
mark.edwards2@uhs.nhs.uk
(ORCID 0000-0002-5048-1784)

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ABSTRACT

OBJECTIVES

To evaluate the clinical effectiveness and safety of a perioperative algorithm for cardiac output-guided haemodynamic therapy in patients undergoing major gastrointestinal surgery.

DESIGN

Multicentre randomised controlled trial.

SETTING

Surgical services of 55 hospitals worldwide.

PARTICIPANTS

2498 adults aged ≥65 years with an American Society of Anesthesiologists physical status classification of II or greater and undergoing major elective gastrointestinal surgery, recruited between January 2017 and September 2022.

INTERVENTIONS

Participants were assigned to minimally invasive cardiac output-guided intravenous fluid therapy with low dose inotrope infusion during and four hours after surgery, or to usual care without cardiac output monitoring.

MAIN OUTCOME MEASURES

The primary outcome was postoperative infection within 30 days of randomisation. Safety outcomes were acute cardiac events within 24 hours and 30 days. Secondary outcomes were acute kidney injury within 30 days and mortality within 180 days.

RESULTS

In 2498 patients (mean age 74 (standard deviation 6) years, 57% women), the primary outcome occurred in 289/1247 (23.2%) intervention patients and 283/1247 (22.7%) usual care patients (adjusted odds ratio 1.03 (95% confidence interval 0.84 to 1.25); P=0.81). Acute cardiac events within 24 hours occurred in 38/1250 (3.0%) intervention patients and 21/1247 (1.7%) usual care patients (adjusted odds ratio 1.82 (1.06 to 3.13); P=0.03). This difference was primarily due to an increased incidence of arrhythmias among intervention patients. Acute cardiac events within 30 days occurred in 85/1249 (6.8%) intervention patients and 79/1247 (6.3%) usual care patients (adjusted odds ratio 1.06 (0.77 to 1.47); P=0.71). Other secondary outcomes did not differ.

CONCLUSIONS

This clinical effectiveness trial in patients undergoing major elective gastrointestinal surgery did not provide evidence that cardiac output-guided intravenous fluid therapy with low dose inotrope infusion could reduce the incidence of postoperative infections. The intervention was associated with an increased incidence of acute cardiac events within 24 hours, in particular tachyarrhythmias. Based on these findings, the routine use of this treatment approach in unselected patients is not recommended.

TRIAL REGISTRATION

ISRCTN Registry ISRCTN39653756.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies suggest that protocolised administration of intravenous fluids and inotropes guided by cardiac output monitoring can reduce complications after major surgery

Definitive evidence is, however, lacking

WHAT THIS STUDY ADDS

A perioperative haemodynamic therapy approach incorporating cardiac output-guided intravenous fluid therapy with low dose inotrope infusion does not reduce the incidence of postoperative infections in high risk patients undergoing major gastrointestinal surgery

Use of fixed, low dose inotrope infusions within such algorithms should be avoided owing to the risk of arrhythmias

Routine use of this intervention is not warranted in unselected patients undergoing gastrointestinal surgery

Introduction

An estimated 310 million patients undergo surgery worldwide each year.[1] Older patients with comorbidities undergoing gastrointestinal surgery have a particularly high burden of postoperative morbidity.[2 3] Around one third will develop a postoperative infection and about 10% will die within six months of surgery.[4] Administering intravenous fluids and inotropic or vasoactive drugs is a central element of perioperative care that may affect patient outcomes.[5-7] Optimal haemodynamic management should provide adequate organ perfusion while minimising iatrogenic harm. However, clinical practices vary widely,[5] and their effect on outcomes remains uncertain.

Protocolised haemodynamic management guided by monitoring of cardiac output is one approach that may improve patient care by reducing the risk of postoperative infections and other complications.[4 8] Our previous studies described the physiological and pharmacological basis of this effect, including the role of low dose inodilators, finding beneficial changes in inflammatory pathways and improved tissue perfusion and oxygenation.[9 10] These are important determinants of postoperative infections.[11 12] Cardiac output-guided therapy has proved controversial at times, and excessive early pulmonary artery catheter

use generated safety concerns.[13-15] More recent trials using simpler, minimally invasive technologies that track changes in cardiac output and stroke volume, using pulse wave analysis and other methods,[16] have resolved some of these safety issues. Clear evidence of clinical effectiveness is, however, still lacking. The results of the original Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) trial of this intervention, although not definitive, highlighted a possible reduction in postoperative infections, but also raised questions about cardiac safety.[4] Meta-analyses further suggest a reduction in postoperative infections and other complications, and shorter hospital stays,[4 6 8] but they are limited by the inclusion of many older, single centre trials with a high risk of bias. This has led to partial adoption and widespread variation in clinical practice.[17]

To address this knowledge gap, we conducted the OPTIMISE II trial of a cardiac output-guided haemodynamic therapy intervention in patients with an increased risk of complications undergoing major elective gastrointestinal surgery. We hypothesised that this intervention would reduce postoperative infections compared with usual clinical care.

Methods

Trial design

OPTIMISE II was an international, multicentre, randomised trial conducted in 55 hospitals in the UK (n=14 hospitals), Spain (n=9), Brazil (n=7), Canada (n=5), US (n=5), Germany (n=4), Poland (n=4), Australia (n=3), Switzerland (n=2), Jordan (n=1), and Romania (n=1). Recruitment ran from 26 January 2017 to 13 September 2022. We compared usual care versus cardiac output-guided intravenous fluid therapy with low dose inotrope infusion, during and four hours after major elective gastrointestinal surgery. The trial design and rationale have been reported previously.[18] The trial protocol (see supplement 1) was approved by the UK National Research Ethics Service (ID 209688) and by responsible ethics committees in all participating countries.

Patients

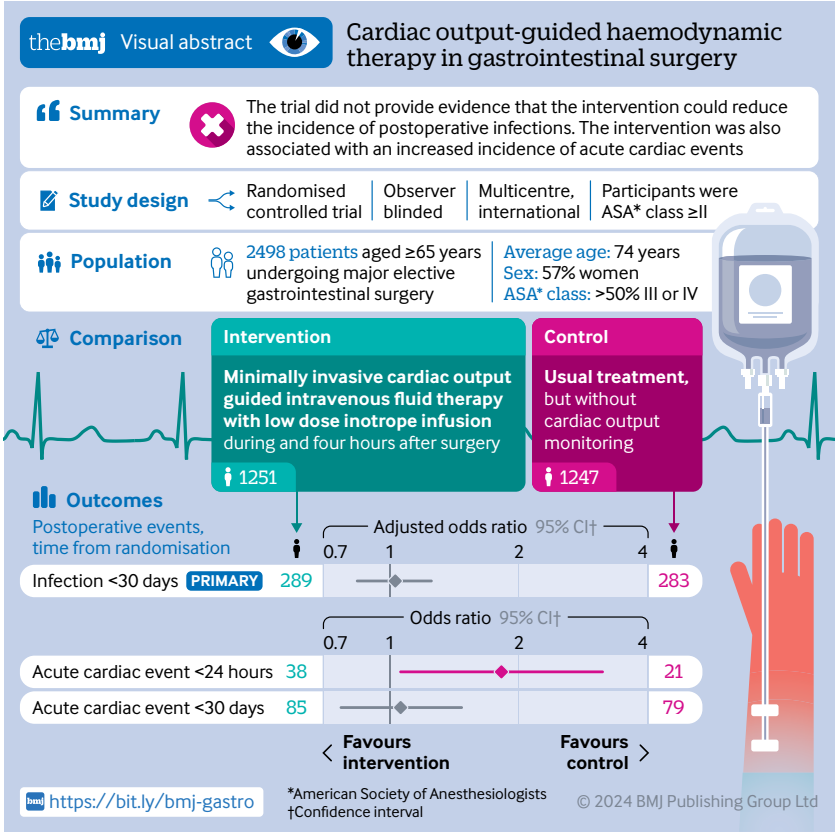
We included patients aged 65 years and older, with an American Society of Anesthesiologists (ASA) physical status classification of II or greater, undergoing major elective surgery involving the gastrointestinal tract with an expected duration of more than 90 minutes. Surgical procedure categories were 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. Exclusion criteria were refusal of written informed consent, clinician refusal, expected mortality <30 days, acute myocardial ischaemia or acute pulmonary oedema in previous 30 days, contraindication to low dose inotropic drugs, 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. All participants provided written informed consent.

Randomisation and masking

After enrolment and shortly before surgery, participants were randomised in a 1:1 ratio by minimisation with a random component (80% probability to be allocated to the group that minimises the between group differences in the minimisation factors), using a central online service, which concealed the allocation sequence. Minimisation variables were country of participating hospital, category of surgical procedure, and ASA class (see supplement 2 for categories). It was not possible to conceal study group allocation during the trial intervention period. Research staff collecting and assessing clinical outcomes were not involved in the participants' care and were unaware of study group allocation. Self-assessment of assessor blinding was performed after follow-up visits. The local principal investigator or delegate unaware of group allocation confirmed the clinical outcomes. Only the independent data monitoring and ethics committee had access to trial data represented by treatment arm. Final analysis was performed after the statistical analysis plan (see supplement 2) was signed off, and the trial database was locked.

Procedures

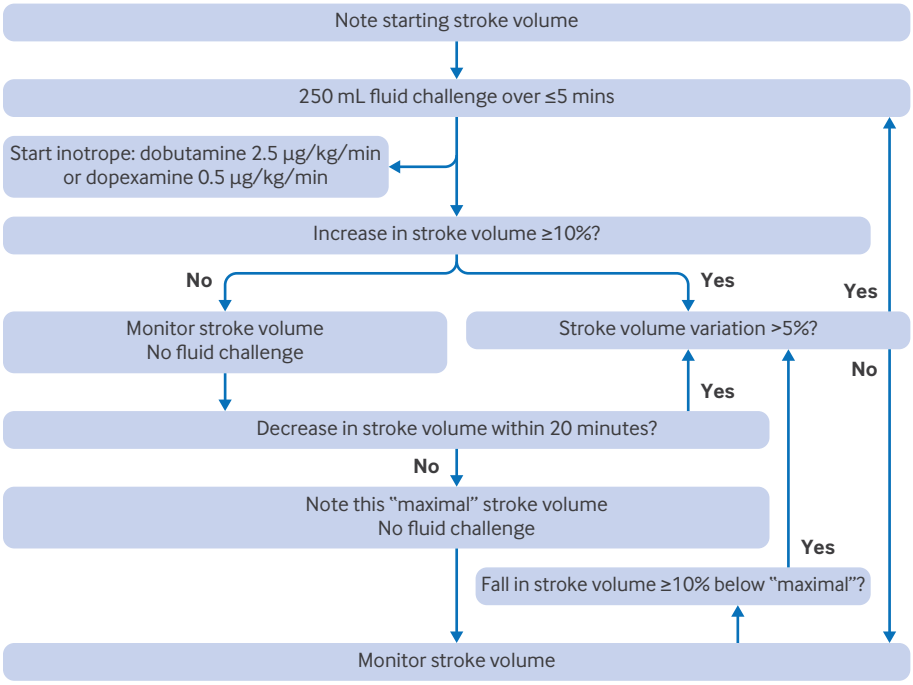
Care for all participants was loosely defined to avoid extremes of practice and practice misalignment while



reflecting the heterogeneity of routine clinical care.[19] Standard treatments were recommended to maintain oxygenation (SpO_2 ≥94%), haemoglobin concentration (>80 g/L), core temperature (37°C), heart rate (<100 beats/min), and mean arterial pressure (60-100 mm Hg). Maintenance fluid requirements were met by a 1 mL/kg/h infusion of crystalloid, with 5% dextrose recommended to minimise salt overload. Clinicians chose from a range of crystalloids or colloids for plasma volume expansion. Anaesthesia and analgesia were provided according to clinician preference and local protocols. Antibiotic prophylaxis was given in accordance with local protocols. Supplement 3 provides details of the trial's standard operating procedures for the care of participants in the intervention and usual care groups.

The trial intervention began after induction of anaesthesia and continued until four hours after surgery (fig 1). Cardiac output and associated haemodynamic variables were monitored using an Edwards Lifesciences (Irvine, CA) system comprising an EV1000 or HemoSphere monitor with either ClearSight (non-invasive) cuff or FloTrac (invasive arterial pressure) sensor depending on clinician choice. The cardiac output monitoring system was set up immediately after the induction of anaesthesia, with cardiac stroke volume measured for the first time post-induction. In addition to maintenance fluids, 250 mL fluid boluses were given in accordance with an algorithm to achieve an optimal value of stroke volume. Ongoing responsiveness to fluid was indicated by a 10% rise in stroke volume after a fluid bolus was administered. Cardiac output was considered optimal when the criteria for fluid responsiveness were no longer met and the stroke volume was maintained for at least 20 minutes. Further fluid boluses were withheld at this point. Additionally, stroke volume variation of <5% was taken to indicate the patient would not be fluid responsive,[20] and fluid boluses were withheld. Intervention group participants also received a fixed, low dose, equipotent infusion of either dobutamine (2.5 µg/kg/min) or dopexamine (0.5 µg/kg/min), chosen based on clinician preference and local availability, and started after the first fluid bolus. If participants developed a tachycardia (>100 beats/min) for 30 minutes despite adequate anaesthesia and analgesia, the inotrope dose was reduced, and was terminated if the tachycardia persisted.

Participants in the usual care group received treatment as usual, but without cardiac output monitoring. At the discretion of the clinician, 250 mL fluid boluses were given guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate, and base excess. Cardiac output monitoring could only be requested to guide the care of participants who became critically unwell during the intervention period. Predefined protocol deviations were failure to use cardiac output monitoring, failure to administer inotrope, or incorrect dose of inotrope administered (intervention group



General haemodynamic measures (all patients)
1. Maintenance fluid at 1 mL/kg/h - dextrose 5% recommended
2. Tranfuse 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 mm Hg; SpO_2 ≥94%; temperature 37°C; heart rate <100 beats/min

Fig 1 | Algorithm for cardiac output-guided haemodynamic therapy for participants in the intervention group. The listed general haemodynamic measures were applied to all trial participants (intervention and control groups)

participants), or the use of cardiac output monitoring in a control group participant.

Outcomes

The primary outcome measure was postoperative infection within 30 days of randomisation, defined using US Centers for Disease Control and Prevention criteria as one or more of superficial, deep, or organ space surgical site infection, pneumonia, urinary tract infection, laboratory confirmed bloodstream infection, or infection of uncertain source. The primary outcome was assessed using information from the medical record and from contact with patients.

Secondary outcomes were acute kidney injury (Kidney Disease Improving Global Outcomes stage 2 or greater[21]) within 30 days and mortality within 180 days of randomisation. The two safety outcomes were acute cardiac events (arrhythmia, myocardial infarction, myocardial injury after non-cardiac surgery, cardiac arrest with successful resuscitation, or cardiogenic pulmonary oedema) within 24 hours and 30 days of randomisation. Process measures were duration of postoperative hospital stay and number of days alive and not in a critical care bed within 30 days of randomisation. Mortality was established by medical record review or from national databases. All morbidity outcomes were defined as events of Clavien-Dindo grade II or higher (ie, requiring clinical treatment) meeting the criteria of recommended standards for perioperative trials.[21-23]

The data monitoring and ethics committee reviewed unblinded data at intervals, including the rate of acute cardiac events as a safety outcome and all other reported serious adverse events. No formal interim analysis was conducted.

Statistical analysis

We determined that a sample size of 2502 participants (1251 in each group) would allow detection of a reduction in postoperative infection rate within 30 days, from 30% to 24% with >90% power, using a two sided test with significance level α=0.05.[4]

All analyses were performed on an intention-to-treat basis, whereby all patients with a recorded outcome were included in the analysis and analysed according to the treatment to which they were randomised. The primary outcome was analysed using a mixed effects logistic regression model with a random intercept for country and fixed effects: surgical procedure category, age, sex, ASA class, and baseline haemoglobin and creatinine levels.[24] We included ASA class and procedure as categorical variables using the same categories used in the minimisation algorithm. We used restricted cubic splines with three knots and knot locations based on Harrell's recommendations to adjust for age and baseline haemoglobin and creatinine levels.[25] A further post hoc analysis of the primary outcome using minimal adjustment including only the minimisation variables (country, surgical procedure category, ASA class) was also conducted during editorial review. Mean imputation was used to account for missing baseline data.[26] The same model was used to analyse safety and secondary outcomes. A secondary analysis was conducted for the primary outcome, which included mortality as a competing risk for postoperative infection in a time-to-event model. All statistical tests were two sided, and we considered a P value <0.05 to be statistically significant. Analyses of heterogeneity of effects across subgroups (surgical procedure category) were assessed by performing a likelihood ratio test comparing the primary outcome analysis model against the same model with a treatment-by-covariate interaction effect added. Surgical approach (laparoscopic or open) was added as a further subgroup analysis post hoc during editorial review and analysed using the same method, along with a comparison of the primary outcome event rate between the control group and each type of cardiac output sensor used in the intervention arm. The statistical analysis plan (see supplement 2) was finalised before unblinding and analysis and is publicly available (https://optimiseii.org/documents).

Patient and public involvement

Patient and public representatives were involved from the planning stages of the trial. The Royal College of Anaesthetists Patient, Carer, and Public Involvement and Engagement (PCPIE) in Research Group reviewed the OPTIMISE II trial in detail. Detailed feedback from the group informed both the design and the conduct of the trial. Specifically, the group considered the results of the original OPTIMISE trial and whether a larger trial was justified. They considered the effect of hospital acquired infection and stated that this was a clinical outcome of clear and direct relevance to patients. The group also provided detailed advice on the patient experience in the trial, particularly trial consent in the limited period within 24 hours of surgery. This led us to strongly promote recruitment in the preoperative outpatient setting. 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 on issues of safety and the experience of participating patients. The trial steering committee included a lay member, providing independent non-medical input to trial conduct.

Results

Overall, 6693 patients were assessed for eligibility and 2502 participants were enrolled. Without knowledge of study group allocation, the independently led trial steering committee advised excluding four enrolled participants who were randomised incorrectly because they did not meet the inclusion criterion for age. Of the 2498 participants meeting the inclusion criteria, 1251 were allocated to receive cardiac output-guided haemodynamic therapy (intervention group) and 1247 to receive usual care (control group) (fig 2). Intervention groups were well matched at baseline (table 1). Mean age was 74 (standard deviation 6) years and 1432/2498 (57.3%) participants were

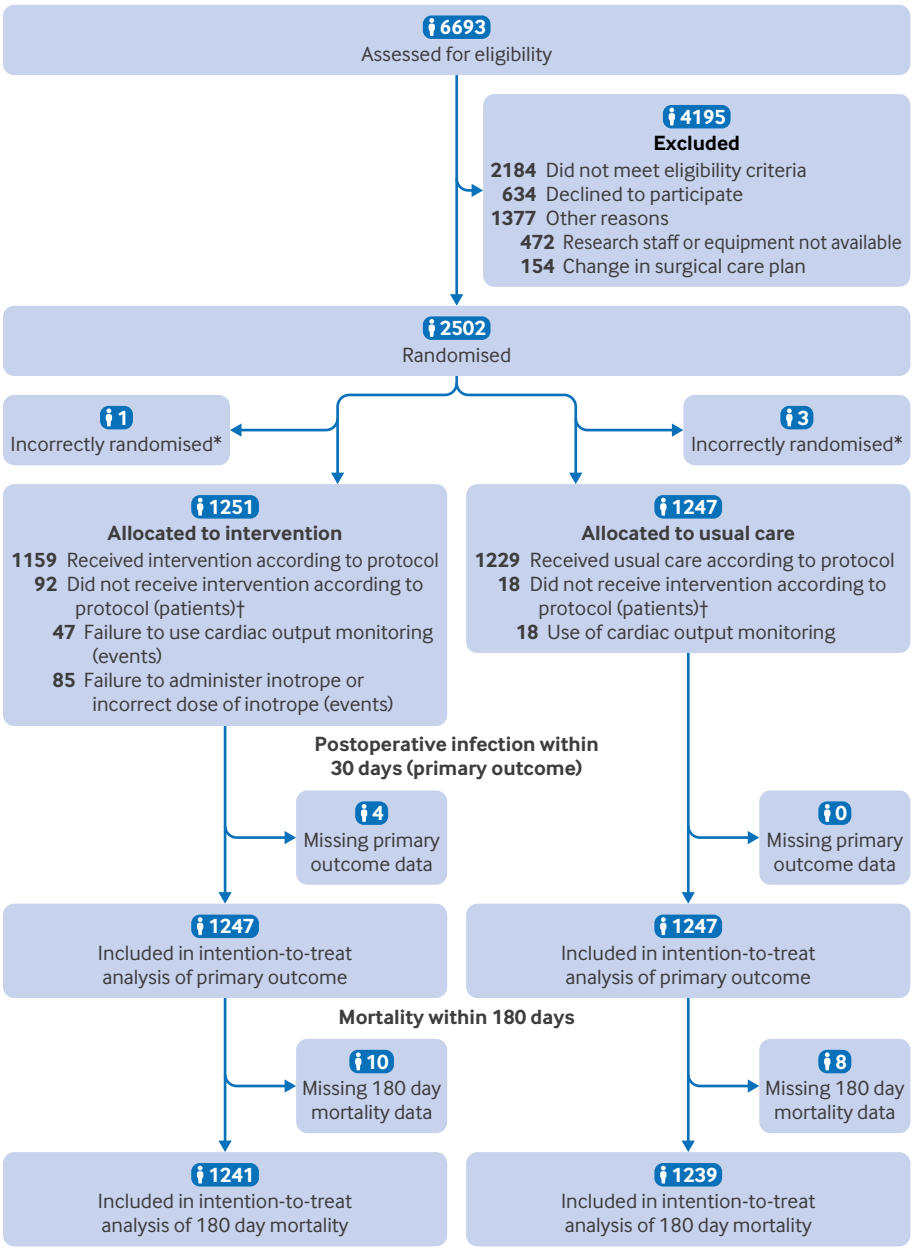


Fig 2 | Flow of participants through study. *After completion of trial recruitment, without knowledge of trial group allocation, the independent trial oversight committees recommended post-randomisation exclusions for incorrect randomisations (patients too young to fulfil inclusion criteria). †Patients could experience more than one predefined protocol deviation category

women. Most surgery types were well represented, and clinical care outside of the trial intervention was similar between the two groups (table 2). The primary outcome was available for 1247 (99.7%) patients in the intervention group and 1247 (100%) patients in the usual care group (fig 2).

Table 2 describes the delivery of the trial intervention. The combined volumes of crystalloid and colloid fluids given during the overall intervention period and within each phase (intraoperative and postoperative) were similar (mean totals for intervention and usual care: 3267 mL *v* 3058 mL, respectively). Balanced crystalloids were the primary fluid used for volume replacement in both groups. Other than the trial inotrope infusion, vasopressors and inotropes were widely used and to a similar extent in both groups. Adherence to intervention was excellent, with 93% of patients receiving trial care that complied with the protocol (see tables S11 and S12 in supplement 3). Trained investigators assisted in administering the trial intervention in 653/1248 (52%) patients during surgery and in 527/1243 (42%) patients during the postoperative phase. Self-assessment showed that investigators were suitably masked for more than 70% of outcomes assessments (see table S10 in supplement 3).

Table 1 | Baseline characteristics of participants. Values are number (percentage) unless stated otherwise

	Summary measure		Absolute standardised difference
	Intervention (n=1251)	Usual care (n=1247)	
Mean (SD) age (years)	74.0 (6.4)	73.9 (6.3)	0.023
Women	714 (57.1)	718 (57.6)	0.009
Mean (SD) BMI	27.2 (5.6)	27.1 (5.2)	0.024
ASA physical status classification*:			
II	607 (48.5)	604 (48.4)	0.002
III	620 (49.6)	617 (49.5)	0.002
IV	24 (1.9)	26 (2.1)	0.012
Mean (SD) haemoglobin (g/L)	124.4 (19.7)	125.6 (19.5)	0.062
Mean (SD) creatinine (µmol/L)	84.5 (49.2)	83.5 (36.1)	0.024
Mean (SD) eGFR (ml/min/1.73m^2)	74.0 (21.4)	74.7 (21.3)	0.032
Comorbidities:			
Chronic obstructive pulmonary disease	133 (10.6)	132 (10.6)	0.002
Asthma	88 (7.0)	87 (7.0)	0.003
Interstitial lung disease or pulmonary fibrosis	14 (1.1)	20 (1.6)	0.042
Ischaemic heart disease	195 (15.6)	167 (13.4)	0.063
Diabetes mellitus	315 (25.2)	322 (25.8)	0.014
Heart failure	62 (5.0)	53 (4.3)	0.034
Liver cirrhosis	31 (2.5)	17 (1.4)	0.081
Planned surgery for active cancer	1054 (84.3)	1043 (83.6)	0.086
Previous stroke or transient ischaemic attack	68 (5.4)	83 (6.7)	0.051
Current smoker (in past 14 days)	117 (9.4)	110 (8.8)	0.019
Preoperative immunosuppressant treatment† <30 days before surgery	81 (6.5)	79 (6.3)	0.005
Positive SARS-Cov-2 test result before surgery‡	1 (0.1)	5 (0.4)	0.066

ASA=American Society of Anesthesiologists; BMI=body mass index; eGFR=estimated glomerular filtration rate; SD=standard deviation.
*ASA physical status classes: I (healthy), II (mild systemic disease), III (severe systemic disease), IV (severe systemic disease that is a constant threat to life), and V (moribund patient not expected to survive without surgery).
†Includes systemic steroids, chemotherapy, or other agents defined in the study protocol.
‡Variable not collected from outset and therefore not available for all participants.

We found no difference between groups in the primary outcome of postoperative infection within 30 days of randomisation, which occurred in 289/1247 (23.2%) intervention patients and 283/1247 (22.7%) usual care patients (adjusted odds ratio 1.03, 95% confidence interval (CI) 0.84 to 1.25; P=0.81). More participants in the intervention group than control group experienced an acute cardiac event within 24 hours (38/1250 (3.0%) *v* 21/1247 (1.7%); adjusted odds ratio 1.82, 1.06 to 3.13; P=0.03) (table 3 and fig 3). This difference was primarily due to a greater number of participants experiencing arrhythmias within 24 hours in the intervention group (33 *v* 17). There was no difference in acute cardiac events within 30 days (85/1249 (6.8%) *v* 79/1247 (6.3%); adjusted odds ratio 1.06, 0.77 to 1.47; P=0.71). Supplementary tables S5 and S6 show the Clavien-Dindo graded severity of cardiac events. Secondary outcomes of acute kidney injury or death within 180 days of randomisation did not differ between the two groups (table 3 and figure S1 in supplement 3). The process measures of hospital stay and days alive and not in a critical care bed within 30 days did not differ between the two groups (see supplement 3, table S1). Tables S4 to S9 and figure S3 in supplement 3 report the components of the primary and secondary outcomes and all other postoperative complications, treatments, and serious adverse event reports, stratified by treatment group.

The prespecified subgroup analysis showed that the effect of the intervention did not differ by category of planned surgical procedure (see table S2 in supplement 3). The post hoc subgroup analyses showed that the effect of the intervention was similar across modes of surgery and the cardiac output monitor sensor technologies available (see table S2 in supplement 3). The primary outcome finding was robust for the effect of mortality acting as a competing risk for postoperative infection (see table S3 and figure S2 in supplement 3), and it was not modified by the post hoc minimally adjusted analysis (table 3).

Discussion

In this trial of 2498 participants at risk of postoperative morbidity, a cardiac output-guided haemodynamic therapy intervention, incorporating optimisation of stroke volume and fixed low dose inotrope infusion, used during and for four hours after major gastrointestinal surgery, did not reduce the incidence of postoperative infections within 30 days. The intervention led to a higher incidence of acute cardiac events within 24 hours of randomisation, owing to an excess of arrhythmias requiring clinical treatment. Study arms did not differ for 180 day mortality, all other safety and morbidity outcomes, or hospital and critical care length of stay. These results did not differ in any prespecified surgical subgroup, nor in the post hoc subgroup analyses by surgical approach or type of monitor sensor technology used.

Interpretation of results and comparison with other studies

It is well established that haemodynamic management during and after surgery, including using intravenous fluid and inotropic or vasoactive drugs, can affect

Table 2 | Clinical management of participants during intervention period (during and for four hours after surgery). Values are number (percentage) unless stated otherwise

	Summary measure	
	Intervention (n=1251)	Usual care (n=1247)
Characteristics of surgery		
Median (IQR) duration of surgery (mins)	259.5 (180-357)	265 (187-365)
Type of surgical procedure:		
Resection of colon, rectum, or small bowel	895 (71.5)	888 (71.2)
Resection of pancreas and bowel	118 (9.4)	115 (9.2)
Resection of stomach (non-obesity surgery)	87 (7.0)	84 (6.7)
Resection of oesophagus (non-obesity surgery)	32 (2.6)	31 (2.5)
Obesity surgery	7 (0.6)	6 (0.5)
Other major surgery involving gut resection	99 (7.9)	114 (9.1)
Surgical technique:		
Open surgical	537 (42.9)	545 (43.7)
Laparoscopic or laparoscopic assisted	607 (48.5)	603 (48.4)
Laparoscopic converted to open	100 (8.0)	93 (7.5)
Cardiac output monitor sensor used:		
ClearSight	236 (18.9)	11 (0.9)
FloTrac	970 (77.5)	2 (0.2)
Other	5 (0.4)	4 (0.3)
Anaesthetic technique:		
General anaesthesia	1248 (99.8)*	1247 (100)
Spinal/epidural	682 (54.5)	649 (52.0)
Tracheal tube removed at end of surgery	1165 (93.1)	1188 (95.3)
Median (IQR) time in post-anaesthesia care unit post-surgery (mins)	240 (60-300)	180 (60-300)
Haemodynamic therapy intervention stopped before 4 hours post-surgery?	59 (4.7)	NA
Level of care on first night post-surgery†:		
Critical care level 3	115 (9.2)	91 (7.2)
Critical care level 2	607 (48.5)	607 (48.7)
Post-anaesthesia care unit	159 (12.7)	162 (13.0)
Surgical ward	364 (29.1)	388 (31.1)
Fluids during surgery		
Primary fluid used for volume replacement:		
Balanced crystalloid‡	1156 (92.6)	1137 (91.2)
0.9% sodium chloride	37 (3.0)	44 (3.5)
Gelatin based colloid	10 (0.8)	5 (0.4)
Starch based colloid	29 (2.3)	28 (2.3)
Albumin	4 (0.3)	0 (0.0)
Other	13 (1.0)	33 (2.7)
Mean (SD) total intravenous crystalloid (mL)	2407 (1810)	2307 (1525)
Mean (SD) total intravenous colloid (mL)	93 (278)	64 (239)
Received any colloid: No (%), mean (SD) volume (mL)	176 (14.1), 661 (418)	147 (11.8), 547 (469)
Mean (SD) total red cell and other blood products (mL)	73 (555)	56 (373)
Received any red cell and other blood products: No (%), mean (SD) volume (mL)	114 (9.1), 802 (1679)	96 (7.7), 731 (1154)
Mean (SD) total volume of all fluids (mL)	2573 (2137)	2428 (1677)
Fluids four hours after surgery		
Primary fluid used for volume replacement:		
Balanced crystalloid	1005 (80.5)	908 (73.1)
0.9% sodium chloride	64 (5.1)	95 (7.6)
Gelatin based colloid	6 (0.5)	3 (0.2)
Starch based colloid	7 (0.6)	4 (0.3)
Albumin	5 (0.4)	1 (0.1)
Other	4 (0.3)	9 (0.7)
None	158 (12.7)	223 (17.9)
Mean (SD) total intravenous crystalloid after surgery (mL)	638 (718)	565 (770)
Mean (SD) total intravenous colloid after surgery (mL)	31 (417)	34 (495)
Received any colloid after surgery, No (%), mean (SD) volume (mL)	38 (3.0), 1016 (2204)	36 (2.9), 1181 (2704)
Mean (SD) total red cell and other blood products after surgery (mL)	26 (409)	31 (493)
Received any red cell and other blood products after surgery, No (%), mean (SD) volume (mL)	27 (2.2), 1191 (2568)	27 (2.2), 1447 (3090)
Mean (SD) total volume of all fluids after surgery (mL)	695 (1336)	630 (1575)
Drugs used during intervention period		
Inotrope infusion:		
Dobutamine	1176 (94.0)	6 (0.5)
Dopexamine	0 (0.0)	0 (0.0)
Neither	68 (5.4)	1241 (99.5)

(Continued)

Table 2 | (Continued)

	Summary measure	
	Intervention (n=1251)	Usual care (n=1247)
Infusion rate reduced due to tachycardia:		
Yes (during surgery)	166 (13.3)	1 (0.1)
Yes (after surgery)	83 (6.6)	1 (0.1)
No	915 (78.6)	11 (84.6)
Bolus vasopressor or inotrope agent used during intervention period§	813 (65.0)	793 (63.6)
Infusion of vasopressor or inotrope (other than intervention mandated fixed dose dopexamine or dobutamine) during intervention period:	505 (40.4)	554 (44.4)
Inotrope infusion	8 (0.6)	12 (1.0)
Vasopressor infusion	504 (40.3)	547 (43.8)
Additional research staff present to assist with trial intervention during surgery	653 (52.2)	142 (11.4)
Additional research staff present to assist with trial intervention in four hours post-surgery	527 (42.1)	81 (6.5)

IQR=interquartile range; NA=not applicable; SD=standard deviation.
*Missing data for three participants. All patients are assumed to have received general anaesthesia owing to extent of surgery
†Levels of care are defined according to care the patient receives: Critical care level 3: includes advanced organ support (eg, invasive ventilation, renal replacement therapy). Critical care level 2: might include advanced cardiorespiratory monitoring (eg, invasive arterial/central venous monitoring) and basic organ support (eg, non-invasive ventilation, inotropic/vasoactive drugs). Post-anaesthetic care unit: designated area for patient care immediately after anaesthesia. Surgical ward (level 0/1): normal ward care without capability for level 2 or 3 interventions or monitoring.
‡Balanced crystalloids included compound sodium lactate/Ringer's solution/Hartmann's solution, Plasmalyte 148, and Normosol-R.
§Inotropes were defined as any of epinephrine (adrenaline), ephedrine, dobutamine, dopexamine, or dopamine. Vasopressors were defined as any of metaraminol, phenylephrine, or norepinephrine (noradrenaline).

postoperative outcomes.[6 7 27] Our findings are at odds with previous research suggesting that perioperative cardiac output-guided haemodynamic therapy reduces infections, other complications, and length of hospital stay after major surgery.[4 6 8] The original OPTIMISE study was previously the largest trial of this intervention (n=734). The primary outcome was a composite of postoperative morbidity events, and the intervention was associated with a relative risk of 0.84 (95% CI 0.71 to 1.01; P=0.07). Of the morbidity components, infections were common overall but appeared less frequent in the intervention group, occurring in 24% of intervention patients and 30% of control patients. A similar reduction in postoperative infections was found when the results were integrated with the results of a previous Cochrane systematic review (relative risk 0.81, 95% CI 0.69 to 0.95).[4] Evidence syntheses have also suggested reductions in the overall incidence of postoperative complications and renal impairment, reduced postoperative hospital stays, and reduced mortality when used in elective surgery.[4 6 8] However, more recent individual trials (each n<1000) have not shown consistent evidence of benefit.[28-31]

Postoperative infections remain one of the commonest surgical complications, with substantial healthcare burden and impact on patients' experience. A large evidence base supports the plausibility of haemodynamic therapy interventions reducing the risk of infections. Surgical site infections are associated with reduced tissue perfusion and tissue oxygenation,[11 12] and our previous work found that this intervention can improve these factors, particularly when low dose inodilators are included in the haemodynamic algorithm.[9 10] Inclusion of these agents is also justified owing to their beneficial modulation of the surgical inflammatory response that may be

Table 3 | Main results for analysis of primary, safety, and secondary outcomes. Values are number (percentage) unless stated otherwise

	No included in analysis		Summary measure		Fully adjusted prespecified primary analysis model			Minimally adjusted analysis model (post hoc)*		
	Intervention (n=1251)	Usual Care (n=1247)	Intervention	Usual Care	Adjusted odds ratio (95% CI)	P value	Adjusted difference in percentage points (95% CI)	Adjusted odds ratio (95% CI)	P value	Adjusted difference in percentage points (95% CI)
Postoperative infection <30 days of randomisation (primary outcome)	1247 (99.7)	1247 (100)	289 (23.2)	283 (22.7)	1.03 (0.84 to 1.25)	0.81	0.4 (−3.4 to 4.2)	1.03 (0.85 to 1.25)	0.75	0.5 (−3.3 to 4.3)
Acute cardiac event <24 hours of randomisation (safety outcome)	1250 (99.9)	1247 (100)	38 (3.0)	21 (1.7)	1.82 (1.06 to 3.13)	0.03	1.3 (0.1 to 2.5)	1.84 (1.07 to 3.17)	0.03	1.4 (0.0 to 2.7)
Acute cardiac event <30 days of randomisation (safety outcome)	1249 (99.8)	1247 (100)	85 (6.8)	79 (6.3)	1.06 (0.77 to 1.47)	0.71	0.4 (−1.6 to 2.3)	1.09 (0.79 to 1.50)	0.61	0.5 (−1.4 to 2.4)
Acute kidney injury <30 days of randomisation	1250 (99.9)	1247 (100)	40 (3.2)	32 (2.6)	1.24 (0.77 to 2.00)	0.37	0.6 (−1.1 to 2.3)	1.26 (0.78 to 2.02)	0.35	0.6 (−1.1 to 2.3)
Mortality <180 days of randomisation	1241 (99.2)	1239 (99.4)	68 (5.4)	84 (6.7)	0.76 (0.54 to 1.07)	0.12	−1.5 (−3.5 to 0.5)	0.79 (0.56 to 1.11)	0.17	−1.3 (−3.1 to 0.6)

ASA=American Society of Anesthesiologists.
*Adjusted for minimisation factors: country, surgical procedure, and ASA class only.

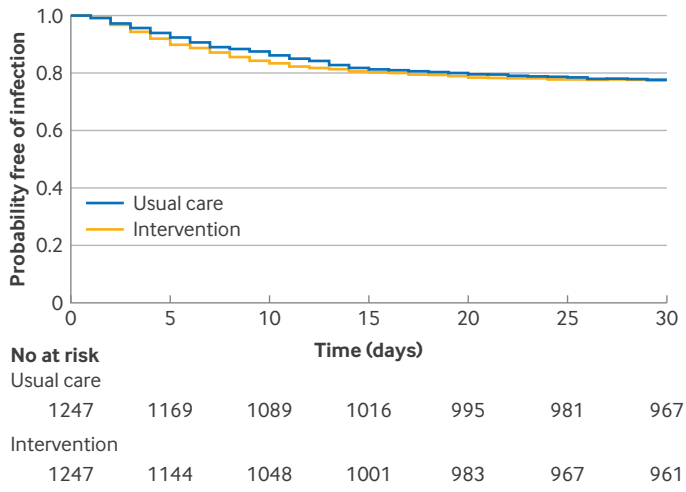


Fig 3 | Kaplan-Meier plot of time to first postoperative infection within 30 days from randomisation

independent of haemodynamic effects.[9] More widely, optimisation of cardiac output-guided stroke volume can maintain adequate gastrointestinal tract perfusion during surgery,[32] helping to maintain barrier function and reduce bacterial translocation, another driver of systemic inflammation and infection.[33] When taken with the previous evidence suggesting modifiability, reducing postoperative infections was therefore the most important beneficial outcome to seek.

Some differences in trial design and setting may explain why our findings contrast with those of existing studies. Most previous trials were smaller, single centre efficacy studies, whereas we studied a simplified haemodynamic intervention in a pragmatic real world clinical effectiveness trial. Infectious and other outcomes have been inconsistently defined in previous research, whereas we used standardised endpoints.[21] Furthermore, much of the research in this area is decades old. In the intervening period, surgical techniques (eg, minimal access), perioperative care (eg, enhanced recovery protocols), baseline infection rates,[4] and other outcomes have improved substantially. Despite using a similar intervention, such non-protocolised changes were seen from OPTIMISE (2014) to OPTIMISE II, with more laparoscopic surgery, less intravenous colloid use, and wider use of non-trial vasopressor or inotrope infusions in this trial. Both fluid composition and maintenance of perioperative blood pressure have been shown to affect postoperative outcomes.[34 35] It is possible that temporal changes in perioperative care have reduced the potential benefits of routinely applied cardiac output-guided haemodynamic approaches when studied in a broad international setting.

The trial intervention included a choice of inotrope. Owing to drug availability, dobutamine was the default inotrope given to intervention patients, whereas dopexamine was routinely used in the original OPTIMISE trial. These agents have subtle differences in haemodynamic, immunomodulatory, and arrhythmogenic effects that may have contributed to our findings.[36] Although the incidence of early perioperative arrhythmias was higher in the current trial's intervention group, by 30 days the number of cardiac events was the same as in the control group, with a lower overall incidence than in the original OPTIMISE trial.[4]

Implications of this study

Given the lack of clinical superiority of this intervention compared with standard care, we do not recommend its routine use in this patient group. With an increased rate of early postoperative arrhythmias, presumably driven by dobutamine, we would advise caution in the use of inotrope infusions in algorithms for perioperative haemodynamic therapy. It remains to be seen whether there are patient groups with characteristics not explored here (eg, demonstrable impairment of cardiovascular performance or particularly high perioperative risk profile) who may derive more benefit. This might apply to subpopulations within this trial (owing to heterogeneity of treatment effect) or to other groups not studied. Our team is currently exploring the role of cardiac output-guided therapy without routine inotrope infusion for patients undergoing emergency abdominal surgery.[37] The results of this trial cannot be extrapolated to that patient group, nor to other specific abdominal surgical groups (eg, liver resection) not included. However, for routine use in elective gastrointestinal surgery, it seems unlikely that further research into similar simple haemodynamic strategies will show a positive effect on postoperative infections. Alternative approaches to perioperative haemodynamic management, such as those based on newer monitoring technologies, personalised blood pressure targets, or more complex algorithms aiming to more closely individualise therapy have shown early benefit, but the effects require confirmation.[35 38-40]

Strengths and limitations of this study

Our study has several strengths. The large sample size and rigorous procedures of the trial addressed the limited statistical power and risk of bias of many previous trials, and the trial groups were well matched. The broad inclusion criteria and international setting enhanced the generalisability of our findings. The haemodynamic strategy we tested was the final iteration of an intervention developed through earlier studies by our team,[4 10 41] with a clear biological rationale for modifying the chosen clinical outcomes. Our previous studies have shown the potentially beneficial effects of incorporating low dose inotropes in modifying immune and inflammatory pathways and in improving microvascular flow and tissue oxygenation.[9 10] The protocol adherence rate was high across diverse international settings, even without the presence of routine research staff or postoperative critical care admission. The inclusion of cardiac safety endpoints provides the highest standard of patient safety data for this intervention. The standardised outcomes definitions and masking procedures during data collection and adjudication helped to minimise

bias. The reporting of self-assessed blinding by data collectors is an important addition. Finally, we used minimisation rather than stratified permuted blocks to randomise patients as this has been shown to offer equivalent or better balance of stratification factors across treatment groups.

Our trial also has some limitations. It was not possible to conceal group allocation during administration of this complex intervention.[4 18] Some elements of wider perioperative care were not standardised or quantified. For example, choice of surgical antibiotic prophylaxis was administered in accordance with local guidelines based on regional resistance patterns, but adherence was not recorded. However, all recorded aspects of non-protocolised perioperative care were similar between trial groups, reducing the likelihood of systemic differences from knowledge of treatment allocation. Both the baseline infection rate and the treatment effect size were lower than assumed for the trial sample size, but we considered the sample size recruited to have been adequate to detect a clinically important difference in the primary outcome. As a large clinical effectiveness trial, we prioritised data collection with a focus on clinical outcomes and adherence and therefore have not reported detailed physiological changes associated with the intervention. However, the physiological effects of similar haemodynamic approaches have already been well characterised in previous efficacy trials. The adherence rate to the intervention was slightly higher in the usual care than intervention group, but this was an expected finding given the intervention was used in addition to treatment as usual. Achieving >90% adherence to an intervention in a large international trial of a multifaceted algorithm is a strength, and it seems unlikely that 100% adherence would have substantially altered our findings. The post hoc subgroup analyses should be considered exploratory and therefore interpreted with caution. In particular, the type of sensor used to monitor cardiac output was chosen after randomisation. The decision to use the non-invasive sensor (ClearSight) may have been biased towards lower risk patients and surgeries and this may in part explain the lower infection rate in this subgroup. Lastly, myocardial injury after non-cardiac surgery is commonly a subclinical event, despite its association with subsequent mortality.[42] We did not routinely screen all participants for myocardial injury after non-cardiac surgery and therefore the true incidence may have been higher than reported.

Conclusion

This international clinical effectiveness trial in high risk patients undergoing major elective gastrointestinal surgery did not provide evidence that cardiac output-guided intravenous fluid therapy with low dose inotrope infusion could reduce the incidence of postoperative infections. The intervention was associated with an increased incidence of acute cardiac events within 24 hours, primarily tachyarrhythmias. The routine use of this treatment approach in unselected patients is not recommended.

Collaborators (*denotes writing committee members): Mark R Edwards,* Rupert M Pearse,* Brennan C Kahan,* Thomas Hamborg,* Garima Priyadarshini,* Neil MacDonald,* Borislava Mihaylova,* Vladimir Gordeev,* Esubalew Assefa,* Priyanthi Dias,* Ann Thomson,* Michael PW Grocott,* Monty G Mythen,* Michael A Gillies,* Michael Sander,* Tuong Phan,* Lisbeth Evered,* Duminda N Wijeysundera,* Stuart A McCluskey,* Andrew D Shaw,* Mitchell Weinstein,* Cesar Aldecoa,* Javier Ripollés-Melchor,* Christoph K Hofer,* Hussein Abu Khudair,* Wojciech Szczeklik,* Ioana Grigoras,* Ludhmila A Hajjar,* Russell Hewson,* Luciana C Stefani,* Sascha Treskatsch,* Michael T Ganter,* Janet van Vlymen,* Mandeep K Phull,* Eric B Lineburger,* Philippe Richebe,* Priyakam Chowdhury,* Míriam de Nadal,* Julia Martínez Ocón,* Ashok Sundar,* Gabrielle Adkins,* Ane Abad-Motos,* Alfredo Abad-Gurumeta,* Anca Irina Ristescu,* Daniel Rusu,* Timothy Martin,* Mareena Joseph,* Anand Lakshminarasimhachar,* Vittoria Arslan-Carlon,* Jai Vairale, Vladislav Burdenov, Anita Patel, Tanjil Nawaz, Tasnin Shahid, Gordon Forbes, Anitha Manivannan, Arouna Woukeu, Mike Waring, Petrea Corcoran, Paul Myles, Jen Reilly, Mayumi Ueoka, Molly Claris, Sarah Robertshaw, Sophie Wallace, Philip Peyton, Aisling Buckley, Gayle Claxton, Sarah Baulch, Saskia Harris, Sofia Sidiropoulos, Abdel Rahman Barhoum, Ali Dabous, Ahmad Arraqap, Ola Yousef, Hatem Al-Jaberi, Mahmoud Al-Masri, Ahlam Hamdan, Aisha Ziedah, Yasmin Safi, Esam Farhoud, Humara Poonawala, Janneth Pazmino-Canizares, Nour Ayach, Matteo Parotto, W Scott Beattie, Marcin Wasowicz, Hance Clarke, Karim Ladha, Angela Jerath, Daniel Sellers, Dallas Duncan, Jo Carroll, Chris Hudson, Samareh Ajami, Saba Ansari, Elham Elsherif, Dorothy Wong, Deep Grewal, Massimiliano Meineri, Louis-Philippe Fortier, Nadia Godin, Oliver Verdonck, Quentin Gobert, Debbie DuMerton, Jessica Shelley, Sheila McQuaide, Melanie Jaeger, Joanna Dion, Hiroaki Sato, Tamaki Sato, Codere Takumi, Thomas Schricker, Ralph Lattermann, Albert Moore, Duane Funk, Stephen Kowalski, Emily Czaplinski, Gabrielle Logan, Marita Monterola, Linda Girling, Angelica Gata, Iulia Jitaru, Madalin Manole, Mariotti Sergio, Marcolino Isabelle, Andreas Winter, Christopher Tsatsaris, Daniela Schneebeli, Daniel Button, Daniel Borer, M Sonsoles Leal, Benigno Rodríguez, Rafael Cabadas, Jesus Rico, Yessica Guerra, Laura Vaquero, Silvia Martin, Alba Herrero, Alba Perez, Carlos Ferrando, María Elena Del Rio, Guido Muñoz, Jaume Balust, Ricard Mellado, Samira Martinez Otero, Alicia Ruiz-Escobar, Barbara Algar-Yañez, Beatriz Nozal-Mateo, Elena Lucena-de-Pablo, Eugenio Martinez-Hurtado, Marina Valenzuela-Peña, Rut Salvachua-Fernández, Sabela Del-Río Fernández, Laura Dos-Santos Carregal, Patricia Doldán Perez, Rosa Soto-Jove De-la-Fuente, Daniel Gomez, Elena Camio, Esther Cano, Ivette Chocron, Patricia Galan, Susana Gonzalez, Ana Pérez-Villafañe, Fernando Díez-Burón, Ana Fernández-Díez, Christina García-Miguel, Rodrigo Pérez-Blanco, Rafael Una, Esther Oviedo, Margarita Perez, Maria Alvarez, Azahara D'avila, Silvia Fernandez, Kane Pryor, Michele Steinkamp, Joydeep Baidya, Julianna Zeepvat, Samantha Huynh, Cheguevara Afaneh, Sheida Tabaie, Aakash Keswani, Angela Mickle, Arianna Montes de Oca, Daniel Park, Divya Mehta, Jordan Oberhaus, Muthuraj Kanakaraj, Swarup Varaday, Thaddeus Budelier, Sherry McKinnon, Ellen Fischbach, Anne Sebastiani, David Monks, Tracy McGrane, Amanda Tilley, Teresa Turnbo, Debbie Craven, Gloria Yang, Mary Fischer, Christine Gillins-White, Alessia Pedoto, Aliaksei Basatski, Anna DiLisio, Athena Christakos, Karah Whatley, Nnamdi Ilonzo, Rupa Chowdary, Zahida Halimi, Marc Royo, Skandan Shanmugan, Annamarie Horan, Lu Cai, Mark Neuman, Andreas Fleischer, Achilles Delis, Alma Puskarevic, Claudia Neumann, Gregor Massoth, Grigorij Schleifer, Maria Wittmann, Markus Velten, Tim Vilz, Vera Guttenthaler, Thomas Grote, Svenja Pabel, Anja Diers, Alien Lipka, Lukas Nannen, Mareike Diekmann, Andreas Weyland, Amir Ali Akbari, Ann-Catrin Paul, Christian Koch, Emmanuel Schneck, Fabian Edinger, Ferdinand Steinsberger, Götz Schmidt, Melanie Markmann, Moritz Herzberg, Sara Denn, Sophie Ruhrmann, Stefan Henkel, Susanne Sanker, Ute Flechtner, Dagmar Schulte, Lukas Habig, Jan Schwiddessen, Rabea Singer, Lennart Junge, Michael Nordine, Nicole Vogel, Philipp Brandhorst, Ralf Trauzeddel, Bernadette Kleikamp, Golschan Asgarpur, Nadine Steinbach-Reimann, Christian Berger, Bartosz Kudliński, Damian Grochulski, Jarosław Zawisza, Magdalena Wirtek, Anna Jelitto, Ryszard Gajdosz, Anna Gajdosz, Jacek Skowronek, Patrycja Kozminska, Pawlik Jaroslaw, Lipska Sylwia, Paweł Grudzień, Aurelia Sega, Anna Mirek, Katarzyna Grzegorzko, Anna Włudarczyk, Bożena Seczyńska, Ilona Nowak-Kózka, Olga Piłat, Suely Zeferino, Filomena Galas, Ligia Camara, Bruna Calil, Jaquelline Jardim, Liana Azi, João Santos, Bianca Santos, Fernando Carvalho, Julian Oliveira, Airton Bagatini, Amanda Sonntag, Tobias Cancian Milbradt, Rubens Devildos Trindade, Alexandre Teruya, Diná Mie Hatanaka, Carolina Baeta Neves Duarte Ferreira, Andre Schmidt, Savio Passos, Rosangela

Minuzzi, Cleiton Pando, Gilberto Braulio, Adriene Stahlschmidt, Claudia Gutierrez, Debora Dornelles, Mariana Brandão, Plinio Leal, Ed Carlos Rey Moura, Sergio Sousa Sena, Amanda Lima Pires, Eduardo Leitao de Almeida Lima, Vitor Fernandes Rios, Bruno Menezes da Rosa da Silva, Leonardo Danielli, Denize Moretti, Danusa de Castro Damasio, Francisco Veras, Luiz dos Reis Falcão, Christian Douradinho, Sul Hwa Shin, Tamas Szakmany, Gemma Hodkinson, Shiney Cherian, Una Gunter, Marc Wittenberg, Christine Eastgate-Jackson, Glykeria Pakou, Helder Filipe, Margaret McNeil, Sara Mingo Garcia, Yvonne Gleeson, Daniel Martin, Toby Reynolds, Donald Milliken, Manuel Pinto, Cassandra George, Christopher Black, Georgios Tsinaslanidis, James Nathan, Lina Kanapeckaite, Rahim Ahmed, Reena Khade, Vasileios Bafitis, Yin Choo, Dorothy Yang, Clare Ivermee, Josephine Cashman, Charlotte Cobain, Ana Robles, Ravisankar Saibaba, Sam Hird, Michael Reay, Andrea Cole, Angela Watts, Clare Allcock, Elena Anastasescu, Karen Reid, Mohamed Mooradun, Ranjit Gidda, Wendy Gardner, Nipun Agarwal, Helen Hollis, Solt Faluveg, Liam Rubents, Karim Salem, Mort Kelleher, Alastair Lang, Heidi Dawson, Jo Singleton, Kate Briton, Katherine Doverman, Lucy Marshall, Maria Amamio, Nicola Rea, Rachael Campbell, Sarah Clark, Scott Simpson, Sophie Birch, Lucy Barclay, Mark Blunt, Melissa Rosbergen, Ruth Hodgson, Tracey Fuller, Kelly Waterfield, Keith Lankester, Linda Ofori, Rose Markes, Samantha Black, Tim Smith, Toni Wilson, Anna McSkeane, Adrian Hodgson, Thomas Sams, Valeria Vasardi, Aparna George, Lace Rosaroso, Rajesh Jain, Tatiana Pogreban, Kalyani Gorrela, George Joseph, Louis Chalmers, Philipa Horne, Nikkita Adams, Caroline Thomas, Aneesha Qadeer, Beverley Jackson, Catherine Moriarty, Naina Stannard, Judith Sharp, Louise White, Michelle Naylor, Rosie Wragg, Samuel Craven, Amrinder Sayan, Jamie Irisari, Nikhil Pawa, Surendini Thayaparan, Philip Barclay, James Armstrong, Valli Ratnam, Robert Thompson, Amanda McGregor, Karen Gray, Patricia Cochrane, Sandra Pirie, Susan Fowler, Christina Coventry, Julie Lochrie, Ross Simmons, David Milne, Hilary Robb, Jayne Ritchie, Sohail Bampoe, Anna Reyes, Chimverly Diaz, Georgia Bercades, Gladys Martir, Samuel Clark, Deborah Smyth, Denise Wyndham, Niall MacCallum, Ernesto Bethin, Max Jonas, Charlie Merry, Clare Bolger, Kirsty Prager, Nikki Collings, Rachel Burnish, Karen Salmon, Amaia Arrieta, Bethan Griffiths, Edyta Niebrzegowska, Fatima Seidu, Filipa Santos, Jan Whalley, Mari-Liis Pakats, Maria Fernandez, Marta Januszewska, Onika Ottley, Salma Begum, Richard Cashmore, Ruzena Uddin, Steven Dunkley, Monica Oliveira.

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Contributors: RMP and MRE conceived the trial. They are responsible for the overall content of the work as guarantors and are considered joint corresponding authors. MRE, RMP, BK, MPG, MGM, VB, and BM contributed to the design of the trial. MRE, RMP, BK, NM, MPG, MGM, VS, BM, PD, AT, MAG, MS, TP, LE, DW, SM, CA, JRM, CH, HA, WS, LH, IG, AS, and MW revised the protocol for important intellectual content. RMP was the chief investigator and MRE was the deputy chief investigator. NM, MS, TP, LE, DW, SM, CA, JRM, CH, HA, WS, LH, IG, AS, and MW acted as national trial coordinators, and all OPTIMISE II investigators implemented and conducted the trial in their local research site supported by PD, AT, and the trial management group (see supplement 3). Oversight was provided by the trial steering committee (majority of independent members) and data monitoring and ethics committee (all independent members). TH and GP directly accessed and verified the underlying data reported in the manuscript and performed the statistical analysis. MRE wrote the first draft of the manuscript, and all members of the writing committee (see supplement 3) revised this draft. All writing committee members read and approved the final version and have final responsibility for the decision to submit for publication. The corresponding authors attest that all listed members of the writing committee meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The trial protocol (see supplement 1) was approved by the UK National Research Ethics Service (IRAS ID 209688) and by responsible ethics committees in all participating countries.

Data sharing: 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 its data sharing policy.

Transparency: The corresponding authors (RMP and MRE) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: A lay summary of the trial results will be made available to participants. For clinical staff, our findings will be widely disseminated at regional, national, and international meetings. We will make use of social media, podcasts, and online Q&A forums to inform the clinical community of the findings and facilitate direct dialogue with clinical staff. For healthcare policymakers, study group members with experience of leading change in perioperative care at a high level will lead a dissemination strategy incorporating UK Department of

Health and Social Care, royal colleges, and NHS trusts, and equivalent organisations in the other countries included. The OPTIMISE II findings will be promoted to guideline committees for inclusion in relevant practice guidance. For patients and members of the public, the study group will facilitate dissemination to patient groups (eg, bowel cancer, inflammatory bowel disease) and provide a lay summary of the trial findings. Inclusion of the findings of OPTIMISE II in an updated Cochrane systematic review is planned, along with a health economic analysis on the healthcare costs and cost effectiveness of the intervention. This will provide a comprehensive package of evidence on this intervention.

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Supplementary information: Supplements 1, 2 (statistical analysis plan), and 3 (supplementary appendix)