Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) Trial

Open, multi-centre, randomised controlled trial of cardiac output-guided fluid therapy with low dose inotrope infusion compared to usual care in patients undergoing major elective gastrointestinal surgery.

Short Title	*OPTIMISE II trial*
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IRAS Reference	*209688*
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Co-Investigator	*Dr Mark Edwards*
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Contents

1. GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
ASA	American Society of Anesthesiologists
CEAC	Cost-Effectiveness Acceptability Curve
CI	Chief Investigator
CRF	Case Report Form
CT	Computed tomography
DMEC	Data Monitoring & Ethics Committee
EQ-5D	Euro-Qol EQ-5D-3L quality of life measure
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IV	intra-venous
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
OR	Odds Ratio
Participant	An individual who takes part in a clinical trial
PCTU	Pragmatic Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

2. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol (version 2.0, 08/12/2020), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator name: Prof Rupert Pearse
Chief Investigator affiliation: Queen Mary University of London

Signature and date:  8th December 2020

Statistician Agreement

The clinical study as detailed within this research protocol (version 2.0, 08/12/2020), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP and the current and applicable regulatory requirements.

Statistician name: Ms Sally Kerry
Statistician affiliation: Queen Mary University of London

Signature and date:  14th January 2021

Principal Investigator Agreement

The clinical study as detailed within this research protocol (version 2.0, 08/12/2020), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator name:
Principal Investigator affiliation:

Signature and date:

3. SUMMARY

Short title	OPTIMISE II trial
Methodology	International, open, multi-centre, randomised controlled trial
Research sites	Surgical services of hospitals undertaking major elective surgery involving the gastrointestinal tract in participating countries.
Objectives	To establish whether the use of minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid, combined with low dose inotrope infusion for patients undergoing major elective surgery involving the gastro-intestinal tract will reduce the incidence of postoperative infection within 30 days of randomisation.
Number of patients	2502 patients (1251 per arm)
Inclusion criteria	Patients aged 65 years and over undergoing major elective surgery involving the gastrointestinal tract that is expected to take longer than 90 minutes.
Exclusion criteria	Patient refusal, clinician refusal, American Society of Anesthesiologists score of I, patients expected to die within 30 days, acute myocardial ischaemia in previous 30 days, acute pulmonary oedema in previous 30 days, any contra-indication to low-dose inotropic medication, pregnancy, previous enrolment in the OPTIMISE II trial, current participation in another clinical trial of a treatment with a similar biological mechanism or primary outcome measure.
Statistical analysis	Analyses will be performed on an intention-to-treat basis including all patients with a recorded outcome. Summary statistics for each group, treatment effects, 95% confidence intervals, and p-values will be presented for primary and secondary outcomes, and process measures. The primary outcome of postoperative infection within 30 days from randomisation will be analysed using a mixed-

	effects logistic regression model adjusted for pre-specified covariates with a random intercept for country.
Study duration	74 months

4. INTRODUCTION

Estimates suggest that over 300 million patients undergo surgery worldwide each year with mortality reported between 1 and 4% (1, 2). Complications and deaths are most frequent among high-risk patients, those who are older or have co-morbid disease and undergo major gastrointestinal or vascular surgery. Importantly, patients who develop complications, but survive to leave hospital, suffer reduced long-term survival (3, 4).

It is accepted that intra-venous fluid and inotropic drugs have an important effect on patient outcomes, in particular following major gastrointestinal surgery. Yet, they are commonly prescribed to subjective criteria leading to wide variation in clinical practice. One possible solution is the use of cardiac output monitoring to guide intra-venous fluid and inotropic drugs as part of a haemodynamic therapy algorithm. This approach has been studied for many years and has been shown to modify inflammatory pathways, and improve tissue perfusion and oxygenation (5, 6). Use of haemodynamic therapy algorithms has been recommended in a report commissioned by the Centers for Medicare and Medicaid Services in the USA, and by the National Institute for Health and Care Excellence (NICE) in the UK. A recent Cochrane review, however, has suggested that the treatment benefit may be more marginal than previously believed (7). The current evidence consists primarily of small trials and is insufficient to resolve controversies regarding potential harm associated with fluid excess, myocardial injury and invasive forms of monitoring. As a result, this treatment has not been widely adopted into clinical practice. Hospital Episode Statistics suggest that around 50,000 NHS patients may benefit from this treatment, but data from a major prospective study showed that it is only used in fewer than one third of these cases (2, 8).

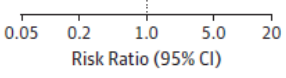
Most recently the multi-centre OPTIMISE trial has been completed; the largest such trial ever performed (9). The intervention algorithm consisted of stroke volume guided fluid therapy and low-dose inotrope (dopexamine) during, and for six hours after surgery. The primary outcome (moderate or major post-operative complications at 30 days) was met by 37% (134 of 366) of patients in the intervention group and by 43% (158 of 364) of patients in the usual care group (relative risk 0.84 [0.71-1.01]; p=0.07). Infective post-operative complications including wound, organ space, lung, urinary or bloodstream infection occurred in 24% of intervention patients compared with 30% of control patients (RR 0.80 [0.63-1.02]; p=0.08). Health economic analysis suggests the intervention was likely to be cost effective (10). The findings of this trial

neither confirm nor disprove the possible benefit of this treatment approach, possibly because the trial was under-powered.

The previous Cochrane systematic review has now been updated with the findings of OPTIMISE and other published trials (9). Complications were less frequent among patients treated according to a hemodynamic therapy algorithm (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0·77 [0·71-0·83]). The intervention was associated with a reduced incidence of post-operative infection (Intervention 182/836 patients [21·8%] vs Controls 201/790 patients [25.4%]; RR 0·81 [0·69-0.95]) and a reduced duration of hospital stay (mean reduction 0.79 days [0.62-0.96]). There was a non-significant reduction in mortality at longest follow-up (Intervention 267/3215 deaths [8.3%] vs Controls 327/3160 deaths [10.3%]; RR 0·86 [0·74-1·00]). However, there remains a risk of bias due to the large number of small trials in the systematic review. More than half the included studies were published more than ten years ago and may not be representative of current practice.

	Intervention		Control					
Source	No. of Events	Total No.	No. of Events	Total No.	Risk Ratio (95% CI)	Favors Intervention	Favors Control	Weight, %
Shoemaker et al,[20] 1988	8	28	30	60	0.57 (0.30-1.08)			1.7
Berlauk et al,[21] 1991	11	68	9	21	0.38 (0.18-0.79)			1.3
Mythen et al,[22] 1995	0	30	6	30	0.08 (0.00-1.31)			0.1
Sinclair et al,[23] 1997	1	20	1	20	1.00 (0.07-14.90)			0.1
Ueno et al,[24] 1998	4	16	5	18	0.90 (0.29-2.78)			0.5
Wilson et al,[25] 1999	38	92	28	46	0.68 (0.48-0.95)			6.2
Lobo et al,[26] 2000	6	19	12	18	0.47 (0.23-0.99)			1.3
Jerez et al,[27] 2001	53	181	65	209	0.94 (0.70-1.28)			7.6
Conway et al,[28] 2002	5	29	9	28	0.54 (0.20-1.40)			0.8
Pearse et al,[14] 2005	27	62	41	60	0.64 (0.46-0.89)			6.3
Wakeling et al,[29] 2005	24	67	38	67	0.63 (0.43-0.93)			4.8
Noblett et al,[30] 2006	1	51	8	52	0.13 (0.02-0.98)			0.2
Donati et al,[31] 2007	8	68	20	67	0.39 (0.19-0.83)			1.3
Smetkin et al,[32] 2009[a]	1	20	4	20	0.25 (0.03-2.05)			0.2
Jhanji et al,[6] 2010	57	90	30	45	0.95 (0.73-1.23)			10.4
Mayer et al,[33] 2010	6	30	15	30	0.40 (0.18-0.89)			1.1
Cecconi et al,[34] 2011	16	20	20	20	0.80 (0.64-1.02)			12.8
Challand et al,[35] 2012	10	89	13	90	0.78 (0.36-1.68)			1.2
Brandstrup et al,[36] 2012[a]	23	71	24	79	1.07 (0.66-1.71)			3.1
Salzwedel et al,[37] 2013[a]	21	79	36	81	0.60 (0.39-0.93)			3.6
Goepfert et al,[38] 2013[a]	34	50	42	50	0.81 (0.65-1.01)			13.7
OPTIMISE, 2014	134	368	158	365	0.84 (0.70-1.01)			21.8
Total	488	1548	614	1476	0.77 (0.71-0.83)			100.0

Heterogeneity: $\chi^2_{21} = 30.44$; $P = .08$; $I^2 = 31\%$
Test for overall effect: $z = 6.22$; $P < .001$



Meta-analysis of number of patients developing complications after surgery (10).

These data highlight the uncertainty surrounding the possible benefits of perioperative haemodynamic therapy algorithms and the need for a definitive large

multi-centre clinical trial to resolve this. The aim of this trial is to evaluate the effects of perioperative haemodynamic therapy guided by cardiac output on the number of patients who develop postoperative infection following major gastrointestinal surgery.

5. TRIAL OBJECTIVES

5.1 Primary objective

To establish whether the use of minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid, combined with low dose inotrope infusion for patients undergoing major elective surgery involving the gastrointestinal tract will reduce the incidence of postoperative infection within 30 days of randomisation.

5.2 Primary outcome measure

The primary outcome is postoperative infection within 30 days of randomisation. This is defined as one or more of the following infections of Clavien-Dindo grade II or greater. A full list of definitions is available in Appendix 1:

i. Superficial surgical site infection;
ii. Deep surgical site infection;
iii. Organ space surgical site infection;
iv. Pneumonia;
v. Urinary tract infection;
vi. Laboratory confirmed blood stream infection;
vii. Infection, source uncertain; this is defined as an infection which could be more than one of the above (i.e. i-vi), but it is unclear which.

5.3 Secondary objectives

To determine whether cardiac output guided haemodynamic therapy reduces mortality, other forms of postoperative morbidity, improves quality of life and is cost-effective.

5.4 Secondary outcome measures

- Mortality within 180 days of randomisation
- Acute kidney injury of Clavien-Dindo grade II or greater, within 30 days of randomisation
- Acute cardiac event of Clavien-Dindo grade II or greater, within 24 hours of randomisation (safety outcome)
- Acute cardiac event of Clavien-Dindo grade II or greater, within 30 days of randomisation (safety outcome)

5.5 Process measures

- Duration of hospital stay (number of days from randomisation until hospital discharge)
- 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 patient is alive and is not in a level 2 or level 3 critical care bed)

5.6 Health economic endpoints (UK only)

- Mean cost from the perspective of NHS at 180 days post-randomisation
- Quality Adjusted Life Years (QALY) at 180 days post-randomisation
- Incremental cost-effectiveness ratio

5.7 Assessment of primary and secondary outcomes

For the primary outcome (postoperative infection of Clavien-Dindo grade II or higher, within 30 days of randomisation), an initial assessment will be made by a research associate; this will typically be a research nurse, but may include physicians and surgeons. The investigator making the assessment should not have been involved in the patient's care, and should be unaware of their treatment group allocation. This initial assessment by the research associate will be based on clinical information including information from patients' medical notes, including (but not limited to) microbiology test results, blood test results, drug prescription charts, radiology tests etc. Patients 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 re-admitted to hospital or seen a doctor since discharge. For patients who have received further treatment or seen a health professional since discharge, further details will be collected directly from the hospital/doctor or from the patient's health records to be used in the research associate's assessment.

If the initial assessment by the research associate is of 'no infection', then the patient's outcome is classified as 'no infection'. If the initial assessment is of 'infection', then this decision must be confirmed by the site Principal Investigator (PI), who will evaluate the information used by the research associate in their initial assessment. The PI's decision is final; they can either confirm the research associate's initial assessment of 'infection' (in which case the patient's outcome is classified as 'infection'), or they can refute it (in which case the patient's outcome is classified as 'no infection'). The PI should only undertake this evaluation if they are unaware of the patient's treatment group allocation. If they are aware of the treatment

allocation, they should delegate this evaluation to a deputy who is unaware of treatment group allocation. The deputy should be a senior clinician. Secondary clinical outcomes (acute kidney injury, acute cardiac event) will be assessed using a similar approach as for the primary outcome.

6. TRIAL METHODOLOGY

6.1 Study design

International, open, multi-centre, randomised controlled trial.

6.2 Inclusion criteria

Patients aged 65 years and over undergoing major elective surgery involving the gastrointestinal tract that is expected to take longer than 90 minutes.

6.3 Exclusion criteria

- Inability or refusal to provide patient consent
- clinician refusal (including intention to monitor cardiac output from the start of surgery regardless of study group allocation)
- American Society of Anesthesiologists (ASA) score of I
- patients expected to die within 30 days
- acute myocardial ischaemia within 30 days prior to randomisation
- acute pulmonary oedema within 30 days prior to randomisation
- contra-indication to low-dose inotropic medication
- pregnancy at time of enrolment
- previous enrolment in the OPTIMISE II trial
- current participation in another clinical trial of a treatment with a similar biological mechanism or primary outcome measure

7. TRIAL PROCEDURES

7.1 Recruitment and screening

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 the relevant nursing and medical staff. Before surgery, potential participants will be identified and approached by a member of the research team, who are considered part of the direct care team. Wherever possible, the patient will be approached at least 24 hours prior to surgery to allow time for any questions. However, by the nature of the inclusion criteria for this trial, many patients will arrive in hospital on the

morning of surgery. Provided that all reasonable efforts have been made to identify a potential participant 24 hours in advance of surgery, they will still be eligible for recruitment within a shorter time frame if this has not proved possible. Written informed consent must be obtained before surgery.

7.2 Informed consent

It is the responsibility of the Principal Investigator (PI) at each site, or persons delegated by the PI to obtain written informed consent from each subject prior to participation in this trial. This process will include provision of a patient information sheet accompanied by the relevant consent form, and an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. The PI or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and consent form will be reviewed and updated if necessary. However, given the short duration of the intervention period, it is most unlikely that new safety information would come to light during the intervention period of an individual patient. Patients who lack capacity to give or withhold informed consent will not be recruited. Patients who are not entered into this trial should be recorded (including reason not entered) on the patient-screening log in the OPTIMISE II Investigator Site File.

7.3 Randomisation

Randomisation will occur after the participant has provided informed consent and shortly before the surgical procedure is due to start. Participants will be centrally allocated to treatment groups in a 1:1 ratio by minimisation with a random component. Minimisation variables will be country, surgical procedure category, and ASA grade. 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; other surgery involving gut resection. The ASA grades 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. To enter a patient into the OPTIMISE II trial, research staff at the site will log on to a secure web-based randomisation and data entry platform hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group. A patient's treatment group allocation will only be revealed to the

person performing randomisation.

7.4 Trial intervention

The trial intervention period will commence at the **start of general anaesthesia** and continue until **four hours after the completion of surgery** (maximum total duration: 24 hours).

Perioperative management for all patients

Care for all patients has been loosely defined to avoid extremes of clinical practice but also practice misalignment (11). All patients will receive standard measures to maintain oxygenation (SpO_2 ≥94%), haemoglobin (>8 g/dl), core temperature (37 °C) and heart rate (<100 bpm). A fluid selected from the Standard Operating Procedure (SOP) for the trial intervention will be administered at 1ml/kg/hr to satisfy maintenance fluid requirements. 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. Mean arterial pressure will be maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilator as required. The trial interventions will commence with induction of anaesthesia and continue until four hours after the end of surgery. Post-operative analgesia will be provided at the discretion of the clinician by epidural infusion (bupivacaine and fentanyl), intrathecal opioids (fentanyl, morphine, diamorphine), wound catheter infusion (bupivacaine), patient-controlled analgesia system (morphine, fentanyl, oxycodone), oral analgesics (including morphine or oxycodone) or intra-venous infusion (morphine or fentanyl). If required, post-operative sedation will be provided with propofol or midazolam. The intervention period will last a maximum of 24 hours (although in most cases much less than this).

Intervention group

The intervention will commence from the induction of general anaesthesia and continue for four hours following surgery. Cardiac output and stroke volume will be measured by cardiac output monitor. Investigators may only use commercially available cardiac output monitoring equipment provided by Edwards Lifesciences in this trial. The specific details of the intervention are available in the SOP for the trial intervention. The manufacturers of the cardiac output monitors will provide this technology on loan to trial sites. No more than 500ml of intra-venous fluid will be administered prior to commencing cardiac output monitoring. In addition to the maintenance fluid and blood products described previously, patients will receive

250ml fluid challenges with a recommended solution as required in order to achieve a maximal value of stroke volume. The absence of fluid responsiveness will be defined as the absence of a sustained rise in stroke volume of at least 10% for 20 minutes or more. In addition, patients will receive a low dose inotrope infusion at a fixed rate which 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 patient develops a tachycardia (heart rate greater than 100bpm) for more than 30 minutes despite adequate anaesthesia and analgesia. Data collection and follow-up for such patients will be performed as normal. All other management decisions will be taken by clinical staff.

Usual care group

Patients in the control group will be managed by clinical staff according to usual practice. This will include 250ml fluid challenges with a recommended intra-venous fluid (see SOP for the management of control group patients) 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 mmHg for 20 minutes 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 criteria. However, clinical staff are free to request cardiac output monitoring if this is required to inform the treatment of a patient who becomes critically ill (e.g. because of severe haemorrhage) during the trial intervention period. In this situation a protocol deviation form will be completed.

7.5 Intervention algorithm

General haemodynamic measures

1. **Maintenance fluid at 1 ml/kg/hr**
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; $Sp0_2$ ≥94%; temperature 37°C; heart rate <100 bpm**

Administering fluid to a stroke volume end-point

1. **250ml fluid boluses to achieve a maximal value of stroke volume**
2. **Fluid challenges should not be continued in patients who are not fluid responsive in terms of a stroke volume increase**
3. **Fluid responsiveness is defined as a stroke volume increase ≥10%**
4. **If stroke volume decreases further fluid challenge(s) are indicated**
5. **Persistent stroke volume responsiveness suggests continued fluid loss**
6. **Fluid challenge is not recommended if stroke volume variation is <5%**

Low dose inotrope infusion

1. **Start fixed rate infusion of dobutamine (2.5µg/kg/min) or dopexamine (0.5µg/kg/min) after first fluid challenge.**
2. **Halve dose if heart rate rises to greater than 100bpm for more than 30 minutes.**
3. **Stop infusion if tachycardia persists.**

What if blood or IV fluid is required regardless of stroke volume?

1. **If blood products or additional fluid challenges are required, then stroke volume should still be monitored to identify any change in maximal stroke volume**

7.6 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 patients 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) should not be involved in the patient's care, and should be unaware of treatment group allocation. Those contacting the patient during follow-up (e.g. at day 30) should also be unaware of treatment group allocation. The research associate undertaking the patient follow up will make a self-assessment of their degree of blinding after the visit.

Research staff enrolling patients will not necessarily be blinded to previous allocations but the randomisation method used is not predictable so there is little risk of selection bias (12). 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 is 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.

7.7 Data collection

The following data will be collected from all patients:

Randomisation data

- Checklist to ensure the patient meets the eligibility criteria
- ASA grade
- Planned surgical procedure category
- Planned level of care on the first night after surgery (Appendix 1)
- Trial patient identifier (generated automatically at point of randomisation)

Baseline data

- Diagnosis of chronic lung disease (COPD, asthma, interstitial lung disease)
- Diagnosis of ischaemic heart disease
- Diagnosis of diabetes mellitus
- Diagnosis of heart failure
- Diagnosis of liver cirrhosis

- Diagnosis of active cancer (indication for surgery Y/N)
- Diagnosis of previous stroke or transient ischaemic attack
- Current smoker (smoked within last 14 days)
- Preoperative immunosuppressant therapy within 30 days before surgery
- SARS-CoV-2 test before surgery
- Ethnicity (to calculate estimated glomerular filtration rate)
- Gender
- Age
- Preoperative haemoglobin
- Preoperative creatinine
- Height
- Weight
- NHS number, Date of Birth and Full Name for registry linkage (UK only)
- Residential postcode for registry linkage (UK only)
- Quality of life according to EQ-5D-3L (UK only)

Data collected during trial intervention period

Surgery & Anaesthesia

- Start and end times of anaesthesia
- Surgical procedure performed
- Open or laparoscopic procedure
- Anaesthetic technique
- Endotracheal tube removed at end of surgery
- Cardiac output monitor use
- Hours spent in post-anaesthetic care unit (recovery room)
- Actual level of care on the first night after surgery

Fluids

- Volume and type of intra-venous colloid solution during surgery
- Volume and type of intra-venous colloid solution during four hours after surgery
- Volume and type of intra-venous crystalloid solution during surgery
- Volume and type of IV crystalloid solution during four hours after surgery
- Volume of red blood cell and blood products during surgery

Drugs

- Use and type of inotrope (including start date/time and end date/time)
- Inotrope rate, infusion site
- Other drugs

Research Staff

- Additional staff present to deliver intervention during surgery
- Additional staff present to deliver intervention during four hours after surgery

Follow-up data

- 30 day post-operative infection (≥Clavien-Dindo grade II: see Appendix 1)
- 24 hour and 30 day adverse cardiac events (≥Clavien-Dindo grade II)
- 30 day acute kidney injury (≥Clavien-Dindo grade II)
- Other 30 day postoperative complications (≥Clavien-Dindo grade II)
- Red blood cell transfusion within 30 days after randomisation
- Parenteral nutrition within 30 days after randomisation
- Endoscopic or radiological intervention within 30 days after randomisation
- Repeat surgery within 30 days after randomisation (with indication)
- Unplanned critical care admission to treat complication(s) within 30 days after randomisation
- Planned critical care admission prolonged due to complication(s) within 30 days after randomisation
- Invasive mechanical ventilation after leaving operating room, within 30 days after randomisation
- Date of death (where applicable)
- Duration of hospital stay
- Number of days in level 2 and level 3 critical care within 30 days after randomisation
- Did the patient survive to discharge of primary hospital admission
- Re-admission to hospital within 30 days of randomisation
- Post-operative SARS-CoV-2
- Self-assessment of blinding of investigator that collected follow-up data
- Quality of life according to EQ-5D-3L health status measure (30 days)
- Quality of life according to EQ-5D-3L health status measure (180 days)

7.8 Predefined protocol deviations

- Failure to use cardiac output monitoring in an intervention group patient

- Failure to administer inotrope to an intervention group patient
- Administration of incorrect dose of inotrope to an intervention group patient
- Use of cardiac output monitoring in a control group patient

7.9 Follow-up procedures

To minimise bias, follow-up data will be collected by an investigator who is unaware of the study group allocation. Investigators will review a participant's medical record and contact participants by telephone to conduct brief interviews at 30 and 180 days after surgery. To collect data on secondary outcomes and facilitate the health economic analysis, we will request hospital episode statistics and mortality data from NHS Digital (formerly HSCIC) for participants in England or equivalent national database. Prospective consent for ONS/HES (or equivalent national database) data linkage will be sought before enrolment into the trial.

7.10 Withdrawal of participants

All study participants are free to withdraw from the study at any time. All randomised patients with a recorded outcome will be included in the final analysis on an intention to treat basis, unless a participant specifically asks for their data not to be included.

7.11 Self-assessment of blinding by research staff

Research staff collecting outcomes data will complete a self-assessment to allow us to report the effectiveness of blinding procedures during the trial. They will grade themselves as one of the following options:

- Suitably blinded
- May have known study group allocation
- Definitely knew study group allocation

7.12 End of study definition

The end of the study is defined as the point when the last patient has completed 180-day follow-up. The Data Monitoring and Ethics Committee (DMEC) will monitor safety data throughout the trial, and will routinely meet to assess safety analyses. Based on these results, they could recommend termination of the trial on safety grounds. They will report any concerns to the Trial Steering Committee (TSC), who will inform the Sponsor and take appropriate action, which may include stopping the trial, to address concerns about participant safety. The Research Ethics Committee will be informed in writing if the trial is suspended or terminated early.

7.13 Schedule of assessment

Event/Visit	Screening	Before surgery	24 hrs after surgery	Hospital discharge	30 days after surgery	180 days after surgery
Inclusion/exclusion criteria	x					
Informed consent	x					
Demographic information		x				
Medical history		x				
Height and weight		x				
EQ-5D-3L (UK Only)		x			x	x
Randomisation		x				
Intraoperative information			x			
Fluid and inotropic therapy			x			
Review of medical notes			x	x	x	
Days of ICU and hospital				x		
Telephone contact					x	x
AE/SAE			x	x	x	x
End of trial form						x

8. STATISTICAL CONSIDERATIONS

8.1 Sample size calculation

In order to detect a 5% absolute reduction (from 30% to 25%) for the primary outcome of postoperative infection up to 30 days (a risk ratio of 0.83), with 80% power, and an overall type I error rate of 5%, we require 2502 patients (1251 per arm). This sample size would also allow us to detect an absolute reduction in the primary outcome of 6% (from 30% to 24%) with 92% power.

8.2 Statistical analysis

Analyses will be performed according to intention-to-treat; all patients with a recorded outcome will be included in the analysis, and analysed according to the treatment to which they were randomised (13). Summary statistics by group, treatment effects, 95% confidence intervals, 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 (14). The model will adjust for surgical procedure category, age, gender, ASA grade, baseline haemoglobin, and baseline creatinine. ASA grade and procedure category will be included as categorical variables. The categories for ASA grade are II, III, and IV. The categories for procedure are (a) resection of colon, rectum or small bowel; (b) resection of pancreas and bowel; (c) resection of stomach

(non-obesity surgery); (d) resection of oesophagus (non-obesity surgery); (e) obesity surgery; (f) 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 (15, 16). Missing baseline data will be accounted for using mean imputation (17). P-values <0.05 will be considered statistically significant. A statistical analysis plan will be written prior to data analysis taking place and any member of the trial team having access to unblinded data.

8.3 Health economic analysis

The health economic analysis will compare the incremental cost per quality adjusted life year (QALY) of cardiac output guided haemodynamic therapy for the prevention of postoperative morbidity compared to usual practice. Cost per patient in the intervention and usual care arms will be assessed from the perspective of the NHS. Costs and outcomes will be evaluated over the 180 day horizon of the trial and no discounting will be applied due to the short length of follow-up. The analysis will include the cost of the intervention in addition to the cost of healthcare resources consumed by patients over the 180 day period. The cost of cardiac output monitoring in the intervention arm will be obtained from trial centres. Data on the length of stay during the index admission will be used to estimate the cost of the initial inpatient episode. The cost of subsequent re-admissions to hospital during the 180 day period will be estimated using electronic health records obtained from the NHS Digital Hospital Episode Statistics (HES) database (18). Data obtained from trial centres and HES, including clinical casemix codes (HRG and OPCS-4) and length of stay, will be combined with the NHS Reference Costs inpatient schedule to estimate the cost per episode (19). Inpatient stays in critical care will be costed according to the level of care received using NHS Reference Costs adult intensive care schedule. Outcomes in the cost-effectiveness analysis will be measured in terms of QALY gained estimated using self-reported Euro-QOL 5-dimension (EQ-5D-3L) score collected at baseline, 30 days and 180 days in combination with UK population utility weights (20). QALYs will be calculated using the area under the curve (AUC) approach, taking into account the length of time spent alive during the follow-up period calculated using linked mortality data from the ONS. An assessment of missing data will be performed on the original cost and outcome data. The approach to handling missing data will depend on whether the data are missing due to incomplete follow-up or informative censoring. Appropriate statistical techniques will be applied to fill in missing fields where data are assumed to be missing at random (MAR). The strategy

for handling missing data in the economic analysis will be pre-specified in the health economic analysis plan prior to obtaining the dataset.

The analysis will gauge the additional cost per QALY gained in the intervention arm compared to usual care using an incremental cost-effectiveness ratio (ICER). Although random allocation to treatment group is designed to remove systematic differences in patient characteristics between groups, chance differences in baseline covariates may impact on the endpoints of the economic analysis. Baseline covariate adjustment will be performed by fitting regression models for mean cost and QALYs gained per patient (21). A generalised linear model with a log link and gamma distribution to control for positive skew will be used to estimate mean cost and linear multivariate regression will be used to estimate mean QALYs gained at 180 days follow-up. Cost and QALY gain will be modelled as a function of treatment assignment (as a dummy variable), age, sex, baseline secondary care cost based on inpatient episodes in the 3 months prior to the intervention obtained from HES, baseline EQ-5D-3L scores, ASA grade, haemoglobin and creatinine measured at baseline. Incremental cost and outcome adjusted for baseline differences in covariates between trial arms corresponds to the coefficient on the treatment dummy variable in the regression models.

The estimation of a confidence interval for the ICER statistic can be problematic for the following reasons: i) differences in QALYs between treatment arms tend to be very small, meaning that the denominator in the ratio may be zero or very close to zero, leading to an undefined value for the ICER; ii) high levels of skew due to a tendency for outliers and zero values in patient-level cost data; iii) costs and outcomes cannot be assumed to be uncorrelated. Non-parametric bootstrapping with replacement based on the observed data is an accepted approach to estimating confidence intervals for the ICER (22). The bootstrapping process will be carried out with 5000 iterations based on the original cost and outcome data using Stata/IC to achieve stability for interval estimates. Regression models will adjust for covariate imbalances on each bootstrapped re-sample. Adjusted incremental cost and outcome estimates will then be used to construct the mean and 95% confidence interval for the ICER. The distribution of incremental estimates will be plotted on a cost-effectiveness plane. A cost-effectiveness acceptability curve (CEAC) will plot the probability of cost-effectiveness of the intervention as a function of willingness-to-pay values per additional QALY gained in order to place the intervention in the context of

current acceptable willingness-to-pay levels for new healthcare technology according to the National Institute for Health and Care Excellence (NICE) (23).

8.4 Secondary studies

The OPTIMISE II trial data will be used for secondary studies directly relevant to the core trial objective including the health economic analysis. A prospective statistical analysis plan will be prepared for each secondary study prior to data analysis.

9. RESEARCH ETHICS

The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) as described at the following internet site: http://www.wma.net/en/30publications/10policies/b3/index.html. The trial will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline (January 1997). The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. At sites, all accompanying material given to a potential participant will have undergone an independent Research Ethics Committee review within that country. Full approval by the Research Ethics Committee will be obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site. All members of the trial steering committee will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.

10. DATA HANDLING AND RECORD KEEPING

10.1 Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act (UK), NHS Caldecott Principles (UK), The Research Governance Framework for Health and Social Care (UK), and the conditions of Research Ethics Committee Approval, or corresponding legislation or approvals for a particular participating country or site. The patient's full name, date of birth, hospital number and NHS number (UK) will be collected to allow tracing through national records. The personal data recorded on all documents will be

regarded as confidential. All patient related trial documents are confidential and must be stored securely at each hospital (e.g. patients' written consent forms). The PI must ensure the patient's confidentiality is maintained at all times. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial management team will require access to patient notes for quality assurance purposes and source data verification, but patients' confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

10.2 Data storage

Data will be transcribed on to the paper CRF prior to entry on to the secure OPTIMISE II data entry web portal. Submitted data will be reviewed for completeness and consistency by authorised users within the study group. Submitted data will be stored securely against unauthorised manipulation and accidental loss. Only authorised users at site, or at Queen Mary University of London (sponsor and host of data entry portal) will have access. Desktop security is maintained through user names and passwords. Data back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 1998 (UK).

10.3 Archiving

All trial documentation and data will be archived centrally by the Sponsor in a purpose designed archive facility for twenty years in accordance with regulatory requirements. Access to these archives will be restricted to authorised personnel. Electronic data sets will be stored indefinitely.

10.4 Patient identifiable data

For each participant a unique participant ID and patient initials will be recorded.

UK only: To facilitate linkage to UK national databases for the collection of follow-up data, patient identifiable data will be collected and entered on to the secure data entry web portal. Data will be stored and handled in accordance with the Data Protection Act 1998 (UK). In the event that patient identifiable data needs to be transferred between authorised users, this will occur by email from @nhs.net to

@nhs.net accounts in the UK or equivalent secure email transfer in other countries.

Outside of the UK

No identifiable data is required for the analysis of patients outside of the UK. Data will be stored and handled in accordance with the appropriate data protection legislation for each particular country or site.

11. PRODUCTS, DEVICES AND TECHNIQUES

11.1 Cardiac output-guided haemodynamic therapy

Cardiac output monitors are routinely used in secondary care. For this study, all sites will only use the cardiac output monitoring equipment provided by Edwards Lifesciences. The device comprises of an EV1000 (monitor), ClearSight (non-invasive sensor) and FloTrac (invasive sensor) and clinicians will be able to choose between the two sensors on a patient by patient basis. Please see the Management of Intervention Group SOP for specific details of the intervention.

12. SAFETY REPORTING

12.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporarily associated with study activities. However, OPTIMISE II is a non-CTIMP trial, and all trial interventions 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 AE on the CRF.

12.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation significantly beyond normal inpatient stay for the surgery concerned;
(d) results in persistent or significant disability or incapacity;

An SAE occurring to a research participant should be reported to the sponsor where in the opinion of the Chief Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

OPTIMISE II is an investigation of a perioperative intervention. It is expected that patients undergoing major abdominal surgery will suffer medical complications, with consequences up to and including death. Only complications considered by the CI to be *related to the use of study procedures* and not a typical complication of abdominal surgery should be reported as SAEs.

12.3 Notification and reporting of Serious Adverse Events

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor and the sponsor's representative for that country within 72 hours of learning of the event.

12.4 Reporting a Serious Adverse Event

Individual sites will notify the co-ordinating centre in that country of an SAE by emailing a scanned copy of the supplementary SAE report form to the national co-ordinator. SAEs will be reported within 72 hours and will be forwarded to the sponsor via the UK co-ordinating centre.

12.5 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Research Ethics Committee of this event within three days. The sponsor must be sent a copy of the correspondence with regards to this matter.

12.6 Annual safety reporting

The CI will send the annual progress report to the UK REC and sponsor. For participating sites outside the UK, reports will be submitted as required by the respective national coordinators, with the support of the trial management group.

12.7 Overview of the safety reporting responsibilities

The CI has the overall oversight responsibility. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

13. MONITORING & AUDITING

The Sponsor will have oversight of the trial conduct at each site. The trial team will take day-to-day responsibility for ensuring compliance with the requirements of GCP in terms of quality control and quality assurance of the data collected as well as safety reporting. The OPTIMISE II Trial Management Group will communicate closely with individual sites and the Sponsor's representatives to ensure these processes are effective. A Data Monitoring and Ethics Committee (DMEC) will be appointed (see section 14.3). The PCTU quality assurance manager will conduct a study risk assessment in collaboration with the CI. Based on the risk assessment, an appropriate study monitoring and auditing plan will be produced according to PCTU SOPs. Any changes to the monitoring plan must be agreed by the PCTU QA manager and CI.

13.1 Monitoring the safety and wellbeing of trial participants

The Research and Development departments at each trial site should perform regular audits of research practice. Systems are in place to ensure that all PIs and designees are able to demonstrate that they are qualified by education, training or experience to fulfill their roles and that procedures are in place that assures the quality of every aspect of the trial. The intervention will last less than 12 hours in most cases, therefore it is extremely unlikely that new safety information will arise during the intervention period. Nonetheless should this situation arise, participants will be informed and asked if they wish to discontinue the intervention. If the subjects wish to continue in the trial they will be formally asked to sign a revised approved patient information sheet and consent form. Early termination of trial in response to safety issues will be addressed via the DMEC. Day to day management and monitoring of individual sites will be undertaken via the Trial Management Group composed of the Chief Investigator and supporting staff. They will meet on a regular basis to discuss trial issues.

13.2 Monitoring the safety of investigators

Each site has health and safety policies for employees. All personnel should ensure

that they adhere to health and safety regulations relating to their area of work. The PI will ensure that all personnel have been trained appropriately to undertake their specific tasks. The trial team will complete GCP and consent training prior to start up.

14. TRIAL MANAGEMENT & COMMITTEES

14.1 Trial management group

Day-to-day trial management will be co-ordinated by a trial management group consisting of the Chief Investigator, his/her support staff and members of the PCTU.

14.2 Trial steering committee

The Trial Steering Committee will oversee the trial and will consist of several independent clinicians and trialists, lay representation, co-investigators, and an independent Chair.

Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- approving the final trial protocol;
- major decisions such as a need to change the protocol for any reason;
- monitoring and supervising the progress of the trial;
- reviewing relevant information from other sources;
- considering recommendations from the DMEC and
- informing and advising on all aspects of the trial

14.3 Data monitoring and ethics committee

The Data Monitoring and Ethics Committee (DMEC) is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. During the period of recruitment into the trial the DMEC will monitor safety data and routinely meet to assess safety analyses. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.

15. FINANCE AND FUNDING

The OPTIMISE II trial will be funded by Edwards Lifesciences and the National Institute for Health Research (UK).

16. SPONSORSHIP & INDEMNITY

Queen Mary University of London will act as trial sponsor and provide no fault insurance.

17. PUBLICATION

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. The TSC will agree the membership of a writing committee, which will take primary responsibility for final data analysis and writing of the scientific report. All members of the writing committee will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. Please see OPTIMISE II trial publication charter for further details.

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APPENDIX 1: Definitions

1. Postoperative complications (24)

The primary outcome is postoperative infection of Clavien-Dindo grade II or greater within 30 days of randomisation. This is defined as one or more of the following infections:

i. Superficial surgical site infection;
ii. Deep surgical site infection;
iii. Organ space surgical site infection;
iv. Pneumonia;
v. Urinary tract infection;
vi. Laboratory confirmed blood stream infection;
vii. Source uncertain; this is defined as an infection which is one or more of the above (i.e. i-vi), but it is unclear which.

Patients who die before day 30 without experiencing an infection will be counted as having 'no infection'. This is because death after a different type of complication will be related to a different biological mechanism. Patients who die before day 30 and have experienced an infection will be counted as having an infection. The date of infection is defined as the date a patient first receives treatment for that infection. In cases where there has been more than one infection, only the date of the first infection will be recorded. Infection must be of Clavien-Dindo grade II or greater, as follows:

Clavien-Dindo scale grading:

I. Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention. Anti-emetics, anti-pyretics, diruetics, electrolytes or physiotherapy are not considered a deviation from the normal postoperative course.
II. Requires pharmacological treatment with drugs (including blood transfusion or total parenteral nutrition) other than those excluded from grade I.
III. Requires surgical, endoscopic or radiological intervention.
IV. Life-threatening complication requiring critical care admission
V. Death

Definitions of infections

Surgical site infection (superficial surgical site)

An infection at the surgical incision site which meets the following criteria:

- Involves only skin and sub-cutaneous tissue of the incision and
- The patient has at least one of the following:
  - purulent drainage from the superficial incision
  - organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
  - at least one of the following symptoms or signs of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.
  - diagnosis of an incisional surgical site infection by a surgeon or attending physician

Surgical site infection (deep surgical site)

An infection at the surgical incision site which meets the following criteria:

- Involves deep soft tissues (e.g. fascial and muscle layers) of the incision and
- The patient has at least one of the following:
  - purulent drainage from the deep incision but not from the organ/space component of the surgical site
  - a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following symptoms or signs: fever (>38°C), or localized pain or tenderness. A culture-negative finding does not meet this criterion.
  - an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination
  - diagnosis of an incisional surgical site infection by a surgeon or attending physician

Surgical site infection (organ/space)

An infection at the surgical incision site, excluding the fascia or muscle layers, which appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and the patient has at least one of the following:

- purulent drainage from a drain that is placed through a stab wound into the organ/space
- organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space
- an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
- diagnosis of an organ/space surgical site infection by a surgeon or attending physician

Pneumonia

This is defined as two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

a. new or progressive and persistent infiltrates
b. consolidation
c. cavitation

And at least one of the following:

a. fever (>38°C) with no other recognized cause
b. leucopenia (<4,000 white blood cells/mm^3) or leucocytosis (>12,000 cells/mm^3)
c. for adults >70 years old, altered mental status with no other recognized cause

And at least two of the following:

a. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
b. new onset or worsening cough, or dyspnoea, or tachypnoea
c. rales or bronchial breath sounds
d. worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand)

Urinary tract infection

A positive urine culture of ≥10^5 colony forming units/mL with no more than two species of micro-organisms with at least one of the following symptoms or signs: fever (>38 °C), urgency, frequency, dysuria, supra-pubic tenderness, costo-vertebral angle pain or tenderness with no other recognised cause, identified within a 24-hour period.

Alternatively, the patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathologic examination with one of the following:

a) purulent drainage from affected site;
b) radiographic evidence of infection;
c) physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space;
d) physician institutes antibiotic therapy for an infection of the kidney, ureter, bladder, urethra, or surrounding tissues.

Laboratory confirmed bloodstream infection

An infection which meets at least one of the following criteria but is not related to infection at another site:

- Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site
- Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following:
  a) common skin contaminant cultured from two or more blood cultures drawn on separate occasions
  b) common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes antimicrobial therapy
  c) positive blood antigen test

Infection, source uncertain

An infection which is considered likely to be one of the following but cannot be differentiated because clinical information suggests more than one possible site: Superficial surgical site infection, or Deep surgical site infection, or Organ space surgical site infection, or Pneumonia, or Urinary tract infection, or Laboratory confirmed blood stream infection. There must be a strong clinical suspicion of infection meeting two or more of the following criteria:

1. Core temperature <36°C or >38°C
2. White cell count >12 x 10^9/L or <4 x 10^9/L
3. Respiratory rate >20 breaths per minute or $PaCO_2$ <35 mmHg
4. Pulse rate >90 beats per minute

2. Acute cardiac events

Acute cardiac events comprise the following events which are defined below.

- Arrhythmia
- Myocardial infarction
- Myocardial injury after non-cardiac surgery (MINS)
- Cardiac arrest without successful resuscitation
- Cardiogenic pulmonary oedema

Arrhythmia

Arrhythmia is defined as electrocardiograph (ECG) evidence of cardiac rhythm disturbance.

Myocardial infarction

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:

- Symptoms of ischemia
- New or presumed new significant ST-segment or T-wave ECG changes or new left bundle branch block
- Development of pathological Q-waves on ECG
- Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intra-coronary thrombus at angiography or autopsy

Myocardial injury after non-cardiac surgery (MINS)

Peak Troponin T of 0.03ng/ml or greater, without evidence of a non-ischaemic aetiology (e.g. sepsis). This criterion does not require the presence of an ischaemic feature.

Cardiac arrest with successful resuscitation

Clinical diagnosis of cardiac arrest followed by return of spontaneous circulation for at least one hour.

Cardiogenic pulmonary oedema

Cardiogenic pulmonary oedema is defined as evidence of fluid accumulation in the alveoli due to poor cardiac function.

3. Acute kidney injury

Acute kidney injury is defined as a two-fold increase in serum creatinine or sustained oliguria of < 0.5 ml kg^{-1} $hour^{-1}$ for twelve hours.

4. Other complications to be reported but not analysed as outcome measures

Acute psychosis

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

Acute respiratory distress syndrome

Develops within one week of surgery; and Chest radiograph or computed tomography scan demonstrating bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules; and Respiratory failure not fully explained by cardiac failure or fluid overload; and Oxygenation meets one of the following criteria (note severity still graded according to Clavien-Dindo system):

a. Mild: PaO_2:FiO_2 between 200 and 300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
b. Moderate: PaO_2:FiO_2 between 100 and 200 mmHg with PEEP ≥5 cmH_2O
c. Severe: PaO_2:FiO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Anaphylaxis

Severe, life-threatening, generalized or systemic hypersensitivity reaction.

Anastomotic breakdown

Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localised area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a sub-clinical leak.

Bowel infarction

Clinical diagnosis demonstrated at laparotomy.

Gastrointestinal bleed

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

stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel and colon.

Multi-organ dysfunction syndrome

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

Paralytic ileus

Failure to tolerate solid food or defecate for three or more days after surgery.

Perforated viscus

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

Other postoperative haemorrhage (not gastrointestinal bleed)

Blood loss within 72 hours after the start of surgery which would normally result in transfusion of blood.

Pulmonary embolism

A new blood clot or thrombus within the pulmonary arterial system. Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery.

Stroke

An embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

Other definitions

1. Preoperative immunosuppressive treatment

Preoperative steroids: Regular administration of an oral or parenteral corticosteroid medication (e.g. Prednisone, Decadron) ending within 30 days prior to surgery for a chronic medical condition (e.g. COPD, asthma, rheumatoid arthritis, inflammatory bowel disease). Topical corticosteroids applied to the skin, or corticosteroids

administered rectally or by inhalation are not included. This does not include short course steroids of a duration of 10 days or less.

Preoperative chemotherapy for malignancy: Any chemotherapy treatment for cancer ending within 30 days prior to surgery. Chemotherapy includes, but is not restricted to oral and parenteral treatment with chemotherapeutic agents for malignancies such as colon, breast, lung, and gastrointestinal solid tumours as well as lymphatic and hematopoietic malignancies such as lymphomas, leukaemia, and multiple myeloma. This does not include treatment consisting solely of hormonal therapy (25).

Other immunosuppressive treatment: any other immunosuppressive treatment given by the oral or parenteral route for 10 days or longer ending within 30 days prior to surgery, for chronic inflammatory or auto-immune conditions or transplant. This may include cytostatics (e.g. cyclophosphamide, methotrexate, azathioprine), monoclonal or polyclonal antibodies, calcineurin inhibitors (e.g. cyclosporin, tacrolimus, sirolimus) or others (e.g. mycophenolate, TNF-binding proteins). This does not include drugs administered by the topical, inhaled or rectal route.

2. Level of care after surgery

The level of care should be defined according to the care the patient received rather than the location. For example, a patient receiving level 2 care in a level 3 area should be recorded as receiving level 2 care.

1. Critical care level 3: includes advanced organ support e.g. invasive ventilation, renal replacement therapy.
2. Critical care level 2: may include advanced cardiorespiratory monitoring (e.g. invasive arterial / central venous monitoring) and basic organ support (e.g. non-invasive ventilation, inotropic/vasoactive drug administration).
3. Post-anaesthetic care unit: care within a designated area for the patients in the immediate recovery from anaesthesia. May deliver care at levels 1 to 3.
4. Surgical ward (level 0/1): normal ward care without level 2 or 3 capabilities.