OPTIMISE II

Statistical Analysis Plan

Version: 3.0
Date: 17/01/2023

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1. Administrative Information

Trial registration number: ISRCTN registry - ISRCTN04386758

This SAP is based on protocol version 2.0 (date 08/12/2020)

SAP revision history

Protocol version	Updated SAP version no.	Section number of changes	List of changes from previous version/protocol	Author of change	Date
V1.0	V1.0	n/a	No changes from analysis planned in the protocol	n/a	25/09/2017
V1.0	V2.0	Section 5, Appendix 2, Appendix 3, Appendix 5	See below	Gordon Forbes	27/02/2019
V2.0	V3.0	Section 3, Section 5, Appendix 2, Appendix 5	See below	GP/TH	11/01/2023

Changes from SAP v1.0

- We added a secondary analysis which estimates the effect of the intervention amongst patients who undergo surgery during the follow-up period. This secondary analysis applies to the primary outcome, and to acute cardiac events at 24 hours and 30 days. This analysis is described in section 5. Stata code to implement this analysis has been added to Appendix 3. A table (table 7) for reporting the results of this analysis has been added to appendix 5.
- We added a new appendix (appendix 2) which details how protocol deviations will be derived from the source data.
- We modified table 16 in appendix 5 to include separate lines for “incorrect dose of inotrope” and “inotrope not given”. In v1.0 these were reported combined in one line.
- We added table 17 to appendix 5 which reports reasons for protocol deviations.

Changes from SAP v2.0

- The process outcome measure ‘Duration of hospital stay’ was changed to ‘Number of days from surgery until discharge’
- Rows added to tables 1 & 12 for data collected on SARS-CoV2 infections.

- Added an analysis of the outcome ‘postoperative infection within 30 days from surgery’ (rather than from randomisation) on p16 and added row for this analysis to table 3.
- A column was added to table 3 presenting covariate-adjusted risk difference treatment effect estimates with 95% CIs.

Members of the writing committee

Gordon Forbes wrote the Statistical Analysis Plan, with input from Brennan Kahan, Rupert Pearse and Mark Edwards. Garima Priyadarshini updated the Statistical Analysis Plan with input from Thomas Hamborg and Rupert Pearse.

Timing of SAP revisions in relation to unblinding of data/results

- Version 1.0 of the SAP was written whilst all contributors had no access to unblinded trial data or to trial results.
- Version 2.0 of the SAP was written after GF had access to blinded trial data (i.e. a trial dataset with variable for treatment allocation removed, and any variables that reveal treatment allocation removed). No other contributors had access to the trial dataset or to trial results.
- Version 3.0 of the SAP was written after TH and GP had access to blinded trial data as above. No other contributors had access to the trial dataset or trial results.

Remit of SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the OPTIMISE II trial. Subsequent papers of a more exploratory nature (including those involving baseline data only) will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post hoc or unplanned analyses will be clearly identified in the respective study analysis report.

2. Background and trial design

Study objectives	**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 gastro-intestinal tract will reduce the incidence of postoperative infection within 30 days of randomisation. **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.
Study design	International, open, multi-centre, two arm, parallel group, randomised controlled trial
Setting	Surgical services of hospitals undertaking major elective surgery involving the gastrointestinal tract in participating countries.
Participants	**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 (ASA) 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
Interventions	**Intervention Group** A cardiac output–guided hemodynamic therapy algorithm for intravenous fluid and inotrope (dopexamine or dobutamine) infusion during and for four hours following surgery **Usual Care Group** Patients in the control group will be managed by clinical staff according to usual practice.
Primary outcome measure	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:

	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.

3. Outcome measures

Primary outcome measure

The primary outcome is postoperative infection within 30 days of randomisation as a binary variable (yes=1, no=0). This is defined as one or more of the following infections of Clavien-Dindo grade II or greater, more detail on the definition of each type of infection is available in the OPTIMISE II protocol:

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.

The process for determining whether the primary outcome has been observed or not, or is described as missing is given in Appendix 0.

Secondary outcomes

- 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)

Full definitions of secondary outcome measures can be found in the OPTIMISE II protocol.

Process Measures

- Duration of post-surgical hospital stay (Number of days from surgery 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)

4. Sample size and randomisation

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.

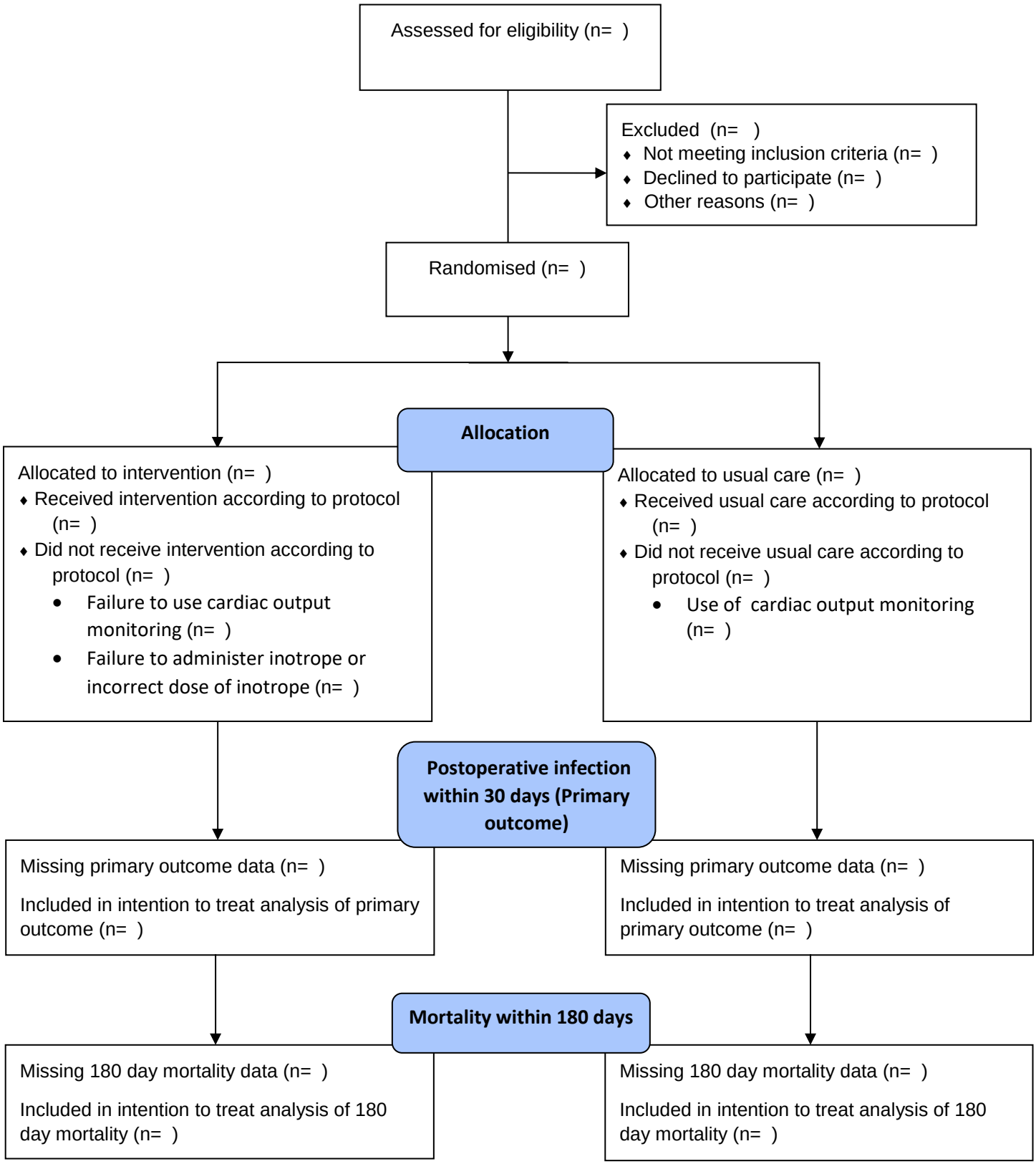
Randomisation procedure

Randomisation will occur after the patient has provided informed consent and shortly before the surgical procedure is due to start. Patients 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 American Society of Anesthesiologists (ASA) grade. The surgical procedure categories are: i) resection of colon, rectum or small bowel; ii) resection of pancreas and bowel; iii) resection of stomach (non-obesity surgery); iv) resection of oesophagus (non-obesity surgery); v) obesity surgery; vi) other surgery involving gut resection. The ASA grades are: II, III, and IV. Each patient will be allocated with 80% probability to the group that minimises the between group differences in these factors among all patients 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.

5. Analysis methods

Information for CONSORT flow diagram

The following information will be provided in the CONSORT flow diagram:



Baseline characteristics

Baseline characteristics will be summarised for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. Draft tables are given in Appendix 5.

General analysis principles

Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis, and analysed according to the treatment to which they were randomised (1). Definitions of what constitutes a recorded outcome for each outcome can be found in Appendix 1. Patients with missing outcome data will be excluded from the analysis. Missing data for baseline covariates to be included in the analysis model will be accounted for using mean imputation (2).

For the analysis of the primary outcome, each secondary outcome, and all process measures, we will present the following information:

- The number of patients included in each analysis, by treatment arm
- A summary statistic of the outcome (e.g. number (%)), by treatment arm
- The estimated treatment effect
- A 95% confidence interval for the estimated treatment effect
- A two-sided p-value

For all analyses, a significance level of 5% will be used.

Analysis of primary outcome

The primary outcome, postoperative infection within 30 days of randomisation, will be analysed using a mixed-effects logistic regression model with a random intercept for country (3), adjusting for planned surgical procedure, ASA grade, gender, age, baseline haemoglobin, and baseline creatinine. Planned surgical procedure and ASA grade will be included as the model as categorical variables. The categories for planned surgical procedure are i) resection of colon, rectum or small bowel; ii) resection of pancreas and bowel; iii) resection of stomach (non-obesity surgery); iv) resection of oesophagus (non-obesity surgery); v) obesity surgery; vi) other surgery involving gut resection. The categories for ASA grade are II, III, and IV. Age, baseline haemoglobin, and baseline creatinine will be modelled using using restricted cubic splines with three knots (with knot locations based on Harrell's recommendations: 10^{th} percentile, 50^{th} percentile and 90^{th} percentile of covariate) (4, 5).

Analysis of secondary outcomes

Mortality within 180 days of randomisation

Mortality within 180 days will be analysed using a mixed-effects logistic regression model with a random intercept for country (3), adjusting for planned surgical procedure, ASA grade, gender, age, baseline haemoglobin, and baseline creatinine. Planned surgical procedure and ASA grade will be included in the model as categorical variables, and age, baseline haemoglobin, and baseline creatinine will be modelled using restricted cubic splines using the same approach as for the analysis of the primary outcome above (4, 5).

Acute cardiac event within 30 days of randomisation

This outcome will be analysed using the same model as 'mortality within 180 days of randomisation' above.

Acute kidney injury within 30 days of randomisation

Acute kidney injury within 30 days will be analysed using a mixed-effects logistic regression model with a random intercept for country (3), adjusting for planned surgical procedure, ASA grade, age, and baseline creatinine. Planned surgical procedure and ASA grade will be included in the model as categorical variables, and age and baseline creatinine will be modelled using restricted cubic splines using the same approach as for the analysis of the primary outcome above (4, 5).

The expected event rate for this outcome is lower than for other outcomes, and as such we have reduced the number of covariates included in the model to ensure a sufficient number of events per variable.

Acute cardiac event within 24 hours of randomisation

Acute cardiac event within 24 hours will be analysed using a logistic regression model, adjusting for ASA grade and age. ASA grade will be included in the model as categorical variables, and age will be modelled using restricted cubic splines using the same approach as for the analysis of the primary outcome above

The expected event rate for this outcome is lower than for other outcomes, and as such we have reduced the number of covariates included in the model to ensure a sufficient number of events per variable.

Analysis of process measures

Duration of post-surgical hospital stay

Duration of post-surgical hospital stay will be analysed using a competing-risk time-to-event model (6), which includes mortality as a competing risk for hospital discharge. The model will include adjustment for planned surgical procedure, ASA grade, gender, age, baseline haemoglobin, and baseline creatinine. Planned surgical procedure and ASA grade will be included in the model as categorical variables, and age, and baseline creatinine will be modelled using restricted cubic splines using the same approach as for the analysis of the primary outcome above (4, 5). Because there are no facilities for analysing competing risk data using mixed-effects models in Stata, we will use robust standard errors which account for clustering by country.

For each treatment arm we will present median and interquartile range for length of hospital stay for patients who survived from surgery to hospital discharge. We will also present for each

treatment arm the number and percentage of patients who survived from surgery until discharge from hospital and number and percentage of patients who died whilst in hospital.

Number of critical care free days up to 30 days from randomisation

Number of critical care free days up to 30 days from randomisation will be analysed using a mixed-effects linear regression model, with a random intercept for country adjusting for planned surgical procedure category, age, gender, ASA grade, baseline haemoglobin, and baseline creatinine. ASA grade and procedure category will be included as categorical variables. Age, baseline haemoglobin, and baseline creatinine will be modelled using restricted cubic splines using the same approach as for the analysis of the primary outcome above (4, 5). Restricted maximum likelihood (REML) will be used.

Analysis method to use if mixed-effects logistic models fail to reach convergence

If the analysis model for the primary analysis or any of the secondary analysis being analysed using mixed-effect logistics models fails to converge the following strategy will be employed:

	Change from previous strategy	**Example Stata code**
0	Primary analysis	`melogit postopinfec_30 i.treat /// i.plan_surg_proc i.asa_grade /// age_spline* haemoglobin_spline* /// creatinine_spline* gender|| country:`
1	Include country as a fixed-effect in place of random effect.	`logit postopinfec_30 i.treat /// i.plan_surg_proc i.asa_grade /// age_spline* haemoglobin_spline* /// creatinine_spline* gender i.country`
2	Remove the fixed-effect for country	`logit postopinfec_30 i.treat /// i.plan_surg_proc i.asa_grade /// age_spline* haemoglobin_spline* /// creatinine_spline* gender`
3	Adjust for age, creatinine and haemoglobin (if included in model) using a single continuous variable	`logit postopinfec_30 i.treat /// i.plan_surg_proc i.asa_grade /// age haemoglobin /// creatinine gender`
4	Remove covariates in the following order. After each covariate is removed the model is run to see if convergence is reached: Gender, baseline haemoglobin, baseline creatinine, planned surgical procedure, age, ASA grade.	`logit postopinfec_30 i.treat /// i.plan_surg_proc i.asa_grade /// age`

Interim analyses

The data monitoring and ethics committee (DMEC) will review outcome data, safety data and recruitment data periodically during the trial. The DMEC will recommend that the trial be stopped early if:

i) There is overwhelming evidence that is likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management.

ii) It becomes evident no clear outcome will be obtained.

No formal stopping rules are in place and no adjustments to the primary analysis will be made to account for any interim analysis performed for the DMEC. To maintain blinding, all unblinded analysis for the DMEC will be performed by an independent statistician who is not otherwise involved in the trial.

Subgroup analyses

A sub-group analysis will be performed for the primary outcome (postoperative infection within 30 days of randomisation) to assess whether the effect of the intervention differs by planned surgical procedure category. The sub-group analysis will be performed using the same analysis model as for the primary outcome, adding an interaction term between planned surgical procedure category and treatment arm. Planned surgical procedure category has six categories: i) resection of colon, rectum or small bowel; ii) resection of pancreas and bowel; iii) resection of stomach (non-obesity surgery); iv) resection of oesophagus (non-obesity surgery); v) obesity surgery; vi) other surgery involving gut resection.

The presence of an interaction will be tested using a likelihood ratio test comparing the sub-group analysis model, including the planned surgical procedure category by treatment interaction, and the primary analysis model, not including the interaction term. The test will be considered significant at the 5% level. All patients with complete outcome data will be included in the subgroup analysis. Within each surgical procedure category, we will report summary statistics of the outcome by treatment arm, and a treatment effects and 95% confidence intervals. A p-value for the interaction test will also be reported.

Sensitivity and secondary analyses

Missing Data

If the level of missing data for the primary outcome exceeds 1% of randomised patients, we will perform a sensitivity analysis to assess the robustness of our analysis of the primary outcome in regard to the data being missing-not-at-random (MNAR). For example, this could occur if patients who were discharged home and had no postoperative infection were less likely to respond to their telephone follow-up after 30 days than patients who did have a postoperative infection.

We define δ_0 and δ_1 as follows:

- δ_0 = assumed event rate amongst patients with missing outcome data in the control arm

- δ_1 = assumed event rate amongst patients with missing outcome data in the control arm

I.e. a value of δ_0=0.3 indicates that we would assume 30% of patients with missing outcome data in the control arm experienced an event (postoperative infection).

We will conduct sensitivity analyses using the following values of δ_0:

- δ_0 = 0.15, 0.2, 0.25, 0.3, 0.35, 0.4

For each value of δ_0, we will use the following values of δ_1:

$\delta_1 = \delta_0 + 0.1,\ \delta_0 + 0.05, \delta_0, \delta_0 - 0.05, \delta_0 - 0.1$

For example, for the scenario where δ_0=0.2 and δ_1=$\delta_0 + 0.1$, we will assume that 20% of patients with missing outcome data in the control arm experience an event, and 30% of patients with missing data in the intervention arm experience an event.

For each different combination of δ_0 and δ_1 we will estimate a treatment effect and 95% CI using the imputation approach outlined below. For each scenario we will perform carry out 10 imputations and combine the results to give one estimate of the treatment effect for that scenario.

Imputation model

For each combination of δ_0 and δ_1 we will impute the missing data as follows. Patients with missing outcome data in the control arm will be randomly ordered within the dataset; the first δ_0 of patients will be set to experiencing an event, and the remaining 1-δ_0 of patients will be set to not having experienced an event. The same approach will be used to impute missing data in the intervention arm.

Analysis model

We will analyse each imputed data set using the analysis model used to analyse the primary outcome (described in the section "Analysis of primary outcome").

Combining estimates from imputed datasets

We will combine estimates of the treatment effect and standard errors from the 10 imputed data sets on the log odds scale using Rubin's rules (7).

Details of Rubin's rules and example Stata code for this sensitivity analysis are given in appendix 4.

Mortality as a competing risk to postoperative infection

To assess the robustness of our primary analysis in regard to mortality acting as a competing risk for postoperative infection we will conduct a competing risk analysis for the primary outcome. Postoperative infection within 30 days of randomisation will be analysed using a competing-risk time-to-event model (6), which recognises mortality as a competing risk for postoperative infection.

The model will adjust for the same baseline covariates as the primary analysis. Because there are no facilities for analysing competing risk data using mixed effects models in Stata, we will use robust standard errors which account for clustering by country.

For each group we will present the median and interquartile range for time to first postoperative infection within 30 days of randomisation, the number (%) of patients who had postoperative infections within 30 days of randomisation, and the number (%) of patients who died before day 30 without having had a postoperative infection. Stata code for this analysis is given in Appendix 3.

Estimating the effect of the intervention for participants who undergo surgery

The main aim of the OPTIMISE II trial is to evaluate whether the intervention improves clinical outcomes compared to control in patients undergoing major elective surgery involving the gastro-intestinal tract. However, in rare instances, surgery may be delayed or cancelled, and so the patient may not undergo surgery before the outcome is collected.

We will therefore conduct a secondary analysis to estimate the effect of the intervention in patients undergo surgery within the follow-up period. This analysis will be conducted for the primary outcome (postoperative infection within 30 days of randomisation), acute cardiac events within 24 hours and 30 days of randomisation.

We will use the method proposed by Bond and White (8) to estimate the effect of the intervention in patients who received surgery. Treatment effects are estimated using a Bayesian method combined with an instrumental variables approach. Full details are provided in Bond and White (8). Briefly, this approach involves specifying an informative prior for the effect of receiving the control intervention compared with receiving no surgery. Uninformative priors are used for all other parameters in the model. The approach can provide valid estimates of the effect of intervention in patients who undergo surgery when the prior for the effect of the control intervention vs no surgery is correctly specified.

In this analysis, we will consider patients who do not undergo surgery within the follow up period for the respective outcome as having not undergone surgery. For the outcomes measured at 30 days (postoperative infection within 30 days, acute cardiac event within 30 days), we will count any patient whose date of surgery is 31 days or more after randomisation as not having received surgery. For acute cardiac event within 24 hours of randomisation we will count anyone whose date of surgery is 2 days or more after the date of randomisation as not having received surgery. Patients for whom the date of surgery is missing will be excluded from the analysis (as will patients with missing outcome data).

Our analysis will be based on a difference in proportions between groups; we opted not to use an odds ratio as our effect measure of interest, as we expected the event rate in the no surgery group to be close to zero for some outcomes, which could lead to difficulties when estimating an odds ratio.

Due to concerns around convergence with small event rates or a low proportion of patients not undergoing surgery, these secondary analyses will not adjust for covariates. In addition, if the event rate across all patients is less than 5% for any outcome, we will not conduct the analysis on this outcome.

Stata code to implement the analysis is available in appendix 3.

In order to allow comparison with the intention to treat estimate, we will conduct an additional ITT analysis for each of the outcomes under consideration (postoperative complications within 30 days, acute cardiac events within 24 hours and 30 days) based on a difference in proportions between treatment groups, unadjusted for covariates. This will be based on a generalised linear model with binomial family and identity link.

Our priors will be based on a normal distribution, with means and variances given in Table A for the effect of the control vs no surgery. To assess the sensitivity of our results to choice of prior we will perform two additional analyses using different priors. Main priors are based on the event rates for the subset of patients in the OPTIMISE I trial who were in the control arm and eligible for OPTIMISE II. We will use the default Stata priors for other parameters in the model. All analyses will be conducted using seed 1234 for the random number generator, with 2500 MCMC burn in, and a 100,000 MCMC sample size (102,500 total MCMC iterations).

Table A – Parameters for priors for effect of usual care vs no surgery

Outcome	**Prior**	**Mean[a]**	**Standard deviation[b]**
Postoperative infection within 30 days of randomisation (primary outcome)	Main	0.31	0.027
	Sensitivity 1 (lower)	0.28	0.027
	Sensitivity 2 (higher)	0.34	0.027
Acute cardiac event within 30 days of randomisation	Main	0.15	0.021
	Sensitivity 1 (lower)	0.12	0.021
	Sensitivity 2 (higher)	0.18	0.021
Acute cardiac event within 24 hours of randomisation	Main	0	0.01
	Sensitivity 1 (higher 1)	0.01	0.01
	Sensitivity 2 (higher 2)	0.02	0.01

[a] This represents the difference in proportions between patients receiving control vs. having no surgery

[b] Based on OPTIMISE I

Estimating the effect of the intervention in the period 30 days from surgery

The sensitivity of the treatment effect in relation to a delayed surgery will further be assessed by repeating the primary outcome analysis using the outcome *postoperative infection within 30 days of surgery*. Participants who did not undergo surgery will be excluded. Number, percentage and postoperative infection rates of participants where date of randomisation and date of surgery differ will be presented.

6. Other analyses, data summaries, and graphs

Other data summaries
Data on the clinical management of patients during intervention period will be summarised for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables.

The individual components of each composite outcome (postoperative infection with 30 days of randomisation, acute cardiac event within 24 hours of randomisation, and acute cardiac event within 30 days of randomisation) will be summarised by treatment arm using the number and percent.

Follow up data collected which is not for primary, secondary or process outcomes will be summarised by treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. Differences between groups will not be presented and no statistical tests will be performed on this data.

For details of summaries see draft tables in appendix 5.

Protocol Deviations
The number and percent of patients with at least one protocol deviation will be summarised for each treatment arm. In addition, in the intervention group this we will provide summaries of the number of patients who did not receive cardiac output monitoring and the number of patients who did not receive inotrope or received the wrong dose. For the usual care group we will summarise the number of patients who received cardiac output monitoring.

Safety analyses
We will report the total number and percent of serious adverse events (SAEs) related to the OPTIMISE II intervention in each treatment group and the number of patients with at least one SAE by treatment group.

Graphs
We will present a Kaplan-Meier plot displaying the survival curve for each treatment arm for postoperative infection within 30 days of randomisation.

We will display the cumulative incidence for postoperative infection up to 30 days of randomisation, taking into account death as a competing risk, based on the competing risks model described in the sensitivity analysis above.

We will display the survival curve for each treatment arm for mortality up to 180 days from randomisation using a Kaplan-Meier plot.

We will display the results of the sensitivity analysis for missing data being MNAR in a graph showing the different treatment estimates and 95% CIs obtained under different assumptions about the event rate in those with missing data.

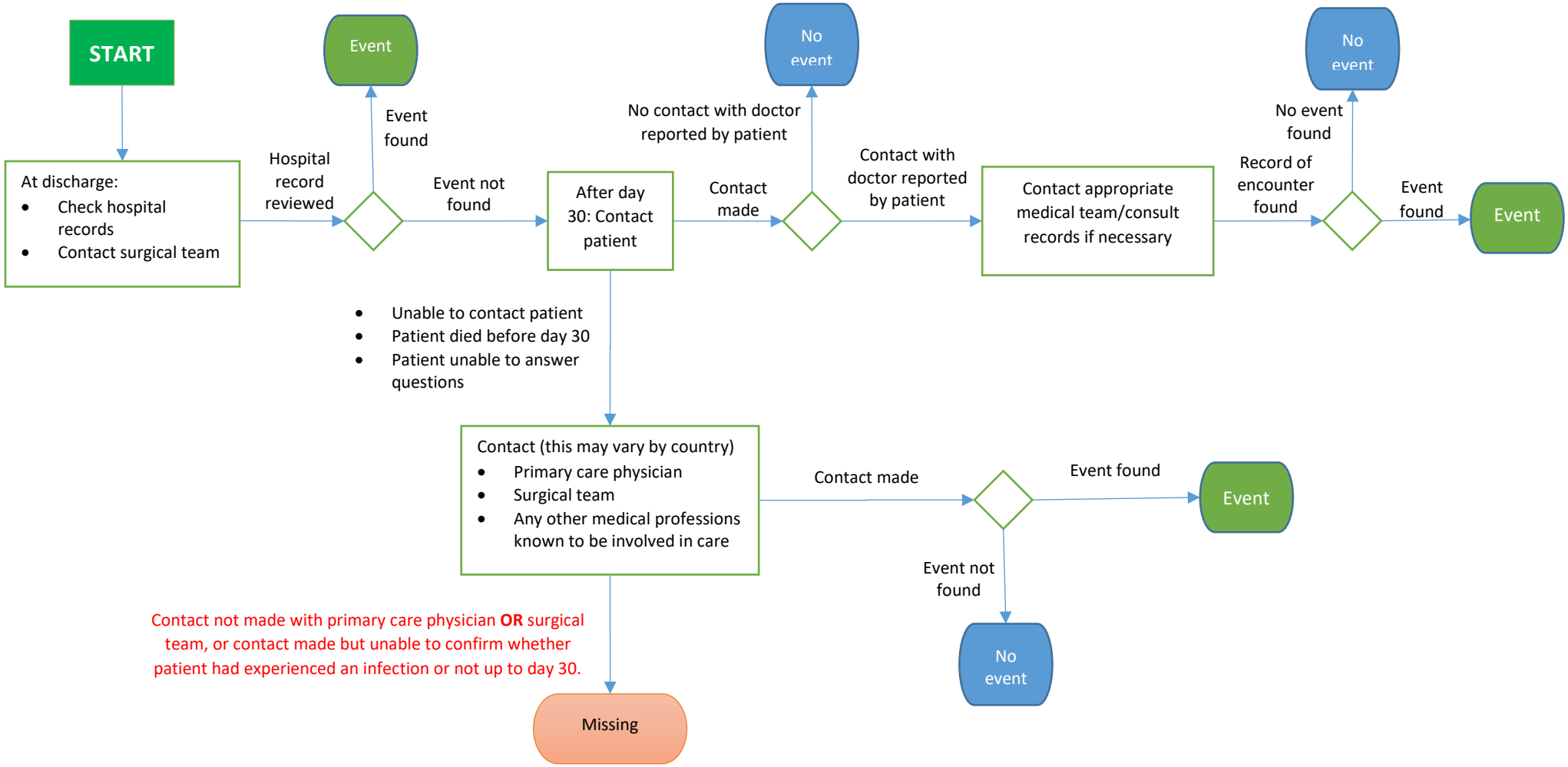
7. References

1. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ. 2011;342:d40.
2. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Statistics in medicine. 2005;24(7):993-1007.
3. Kahan BC. Accounting for centre-effects in multicentre trials with a binary outcome - when, why, and how? BMC medical research methodology. 2014;14:20.
4. Kahan BC, Rushton H, Morris TP, Daniel RM. A comparison of methods to adjust for continuous covariates in the analysis of randomised trials. BMC Med Res Methodol. 2016;16:42.
5. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2001.
6. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999;94(446):496-509.
7. Rubin DB. Multiple imputation for nonresponse in surveys. Hoboken, N.J. ;: Wiley-Interscience; 2004. xxix, 287 p. p.
8. Bond SJ, White IR. Estimating causal effects using prior information on nontrial treatments. Clinical Trials. 2010;7(6):664-76.
9. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? - Some practical clarifications of multiple imputation theory. Prevention Science. 2007;8(3):206-13.

8. Appendices

Appendix 0: Determining primary outcome status

Determining whether a patient has experienced one of the components of the primary outcome will be carried out by the following process:



9. Appendix 1: Deriving outcomes

Primary Outcome

Postoperative infection within 30 days of randomisation

- Equal to 1 if:
  - At least one of the components of postoperative infection is Clavien-Dindo II or greater:
  - AND Date of diagnosis of first postoperative infection is within 30 days of randomisation.
- Equal to 0 if:
  - All of the components of postoperative infection are "None" or Clavien-Dindo I or the date of diagnosis of first infection is after 30 days of randomisation.
- Missing if:
  - All components are missing
  - One or more of the components of postoperative infection is missing and all other components are "None" or Clavien-Dindo I
  - One or more of the components of postoperative infection is Clavien-Dindo II or greater and date of diagnosis of first postoperative infection is missing.

Secondary Outcomes

Mortality within 180 days of randomisation

- Equal to 1 if:
  - Patient status at 180 day follow up is dead
  - AND date of death is within 180 days of randomisation
- Equal to 0 If:
  - Patient status at 180 day follow up is alive
  - Missing if: Patient status at 180 day follow up is missing
  - OR patient status at 180 day follow up is dead and date of death is missing

Acute kidney injury of Clavien-Dindo grade II or greater, within 30 days of randomisation

- Equal to 1 if:
  - acute kidney injury within 30 days of randomisation is Clavien-Dindo II or greater
- Equal to 0 if:
  - acute kidney injury within 30 days of randomisation is none or Clavien-Dindo I
- Missing if:
  - acute kidney injury within 30 days of randomisation is missing

Acute cardiac event of Clavien-Dindo grade II or greater, within 24 hours of randomisation

- Equal to 1 if:

- At least one of the components of acute cardiac event within 24 hours is Clavien-Dindo II or greater.
- Equal to 0 if:
  - All of the components of acute cardiac event within 24 hours are equal to "None" or Clavien-Dindo I
- Missing if:
  - All components are missing
  - One or more of the components of acute cardiac event within 24 is missing and all other components are "None" or Clavien-Dindo I

Acute cardiac event of Clavien-Dindo grade II or greater, within 30 days of randomisation

- Equal to 1 if:
  - At least one of the components of acute cardiac event within 30 days of randomisation is Clavien-Dindo II or greater.
- Equal to 0 if:
  - All of the components of acute cardiac event within 30 days of randomisation are non-missing and equal to "None" or Clavien-Dindo I
- Missing if:
  - All components are missing
  - One or more of the components within 30 days of randomisation is missing and all other components are "None" or Clavien-Dindo I

Process Measures

Duration of post-surgical hospital stay

This outcome will be defined by two variables, the discharge event (discharged/died before discharge), and time to discharge event.

Discharge event

- Patients will be classified as discharged if patient survived to discharge for primary hospital admission.
- Patient will be classified as died before discharge if patient did not survive to discharge for primary hospital admission.
- Discharge event will be missing if item "Did the patient survive to discharge from primary hospital admission?" is missing.

Time to discharge event

- Time to discharge event will be equal to the duration of primary hospital admission - (date of surgery – date of randomisation).
- Time to discharge event will be missing if duration of primary hospital admission is missing or if discharge event is missing.

Number of critical care free days up to 30 days from randomisation

- If patient is alive 30 days from randomisation:
  - equal to 30 – (total duration of level 2 critical stay within 30 days of randomisation + total duration of level 3 critical stay within 30 days of randomisation)
- If patient died within 30 days of randomisation
  - equal to (date of death – date of randomisation) – (total duration of level 2 critical stay within 30 days of randomisation + total duration of level 3 critical stay within 30 days of randomisation).
- Missing if:
  - Total duration of level 2 critical stay within 30 days of randomisation is missing
  - OR total duration of level 3 critical stay within 30 days of randomisation is missing
  - Or Mortality at 30 days is missing

Appendix 2: Protocol deviations

The questions used to determine protocol deviations are in section 4 of the main OPTIMISE CRF, titled "Trial intervention period", under the headings "Cardiac output monitoring" and "Drugs".

Did not receive cardiac output monitoring (intervention group only)

- Deviation occurs if:
  - "Did the patient receive cardiac output monitoring during the trial intervention period" is answered "No"
- Deviation does not occur if either:
  - "Did the patient receive cardiac output monitoring during the trial intervention period" is answered "Yes"
- Deviation missing if "Did the patient receive cardiac output monitoring during the trial intervention period" is missing

Did not receive inotrope (intervention group only)

- Deviation occurs if:
  - "Inotrope infusion used" is answered "Neither"
- Deviation does not occur if either:
  - "Inotrope infusion used" is answered either "Dobutamine" or "Dopexamine"
- Deviation missing if "Inotrope infusion used" is missing

Received incorrect dose of inotrope (intervention group only)

- Deviation occurs if one of the following holds:
  - "Inotrope infusion used" is answered "Dobutamine" and highest rate administered is greater than 2.7 µg/kg/min
  - "Inotrope infusion used" is answered "Dobutamine" and lowest rate administered is less than 2.3 µg/kg/min and "Infusion rate reduced due to tachycardia?" is answered "No"
  - "Inotrope infusion used" is answered "Dopexamine" and highest rate administered is greater than 0.6 µg/kg/min
  - "Inotrope infusion used" is answered "Dopexamine" and lowest rate administered is less than 0.4 µg/kg/min and "Infusion rate reduced due to tachycardia?" is answered "No"

- Deviation does not occur if one of the following holds:
  - "Inotrope infusion used" is answered "Dobutamine" and highest rate administered is less than 2.7 µg/kg/min and lowest rate administered is greater than 2.3 µg/kg/min
  - "Inotrope infusion used" is answered "Dobutamine" and highest rate administered is less than 2.7 µg/kg/min and lowest rate administered is less than 2.3 µg/kg/min and "Infusion rate reduced due to tachycardia?" is answered "Yes (during surgery)" or "Yes (after surgery)"
  - "Inotrope infusion used" is answered "Dopexamine" and highest rate administered is less than 0.6 µg/kg/min and lowest rate administered is greater than 0.4µg/kg/min

    - "Inotrope infusion used" is answered "Dopexamine", highest rate administered is less than 0.6 µg/kg/min, lowest rate administered is less than 0.4 µg/kg/min, and "Infusion rate reduced due to tachycardia?" is answered "Yes (during surgery)" or "Yes (after surgery)"

- Deviation is missing if one of the following holds:
    - Inotrope infusion used is missing
    - Highest rate administered is missing
    - Lowest rate administered is missing and Infusion rate reduced due to tachycardia is not "Yes (during surgery)" or "Yes (after surgery)"
    - Lowest rate administered is less than 2.3 µg/kg/min (dobutamine) or less than 0.4 µg/kg/min (dopexamine) and Infusion rate reduced due to tachycardia is missing

<u>Received cardiac output monitoring (control group only)</u>

- Deviation occurs if:
    - "Did the patient receive cardiac output monitoring during the trial intervention period" is answered "Yes"
- Deviation does not occur if either:
    - "Did the patient receive cardiac output monitoring during the trial intervention period" is answered "No"
- Deviation missing if:
    - "Did the patient receive cardiac output monitoring during the trial intervention period" is missing

<u>Reasons for protocol deviations</u>

Reasons for protocol deviations will be taken from the protocol deviation form. Reasons will only be reported for protocol deviations that occur according to one of the conditions above. If a protocol deviation form is not completed and one of the above conditions for a protocol deviation is met, we will still consider a protocol deviation to have occurred, however the reason will be missing.

Appendix 3: Stata code for analysis

Code for analysis is written to be implemented in Stata 14, with the exception of the analysis estimating the effect of the intervention for participants who undergo surgery, which requires Stata 15 to be implemented.

Analysis of primary outcome

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

melogit postopinfec_30  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender ///
       || country:, or
```

Analysis of secondary outcomes

Mortality within 180 days of randomisation

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

melogit mortality_180  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender ///
       || country:, or
```

Acute cardiac event within 30 days of randomisation

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

melogit ac_cardiac_30  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender ///
       || country:, or
```

Acute kidney injury within 30 days of randomisation

```
mkspline age_spline = age, cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

melogit ac_kidney_30  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* creatinine_spline* ///
       || country:, or
```

Acute cardiac event within 24 hours of randomisation

```
logit ac_cardiac_24h  i.treat ///
       i.asa_grade age
```

Analysis of process measures

Duration of hospital stay

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

stset duration_hosp, failure(discharge)
stcrreg  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender /// ///
       ,compete(death_hosp) vce(cluster country)
```

Number of critical care free days up to 30 days from surgery

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)
```

```
mixed crit_care_free  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender ///
       || country:, reml
```

Subgroup analysis

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

*fitting model including interaction term
melogit postopinfec_30  i.treat##i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender ///
       || country:, or

est store A // storing estimates

*Obtaining treatment effects for subgroups
lincom 1.treat + 1.treat#2.plan_surg_proc, eform
lincom 1.treat + 1.treat#3.plan_surg_proc, eform
lincom 1.treat + 1.treat#4.plan_surg_proc, eform
lincom 1.treat + 1.treat#5.plan_surg_proc, eform
lincom 1.treat + 1.treat#6.plan_surg_proc, eform


*performing likelihood ratio test for interaction
*fit model for primary analysis
melogit postopinfec  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender ///
       || country:, or

est store B // storing estimates

lrtest A B //interaction test
```

Sensitivity analyses: Mortality as a competing risk to postoperative infection

```
mkspline age_spline = age, cubic nknots(3)
mkspline haemoglobin_spline = haemoglobin , cubic nknots(3)
mkspline creatinine_spline  = creatinine , cubic nknots(3)

stset time_to_inf, failure(postopinfec_30)
stcrreg  i.treat ///
       i.plan_surg_proc i.asa_grade ///
       age_spline* haemoglobin_spline* creatinine_spline* gender /// ///
       ,compete(death_30) vce(cluster country)

*graphing cumulative incidence function
stcurve, at1(treat=1) at2(treat=0) cif
```

Secondary analysis - estimating the effect of the intervention for participants who undergo surgery (Stata 15)

```
/*Compliance variables required:

 c_z1: binary indicator equal to 1 if patient is in intervention group and
underwent surgery during the time-frame of the specified outcome, 0 otherwise (and
missing if date of surgery is missing)

 c_z0 binary indicator equal to 1 if patient is in usual care group and underwent
surgery during the time-frame of the specified outcome, 0 otherwise (and missing if
date of surgery is missing)

*/


reg c_z1 treat
predict prob_new_trt
reg c_z0 treat
predict prob_std_trt

/*
Note in the following command the option  "nomleinitial" is required to stop Stata
using a maximum likelihood estimate for initial values. This is not possible due to
the collinearity of the variables in the model. The option "collinear" is required
to supress collinearity check.
*/

bayes, prior ({postopinfec_30: prob_std_trt}, normal(0.31, 0.27)) ///
             nomleinitial rseed(1234) mcmcsize(100000): ///
             binreg  postopinfec_30  prob_new_trt prob_std_trt, rd collinear

bayesstats summary ({postopinfec_30:prob_new_trt} ///
       - {postopinfec_30:prob_std_trt})

bayesgraph diagnostic {postopinfec_30: prob_std_trt} {postopinfec_30: prob_new_trt}
```

Appendix 4: Missing data sensitivity analysis

Rubin's Rules

Estimates and standard errors from the analysis of imputed data sets will be combines using Rubin's rules (7). These are described in an easy to understand format in (9).

For m imputed data sets with treatment estimates $\hat{Q}_i$ with variances $\widehat{var(Q_i)}$ the combined treatment estimate, will be given by $\bar{Q}$, the mean of the m estimates from the imputed data sets:

$$\bar{Q} = \frac{1}{m}\sum_{i=1}^{m}\hat{Q}_i.$$

The estimate of the variance of the overall imputed variance will be calculated by:

$$\text{var}(\bar{Q}) = \bar{U} + \left(1 + \frac{1}{m}\right)B$$

Where $\bar{U} = \frac{1}{m}\sum_{i=1}^{m}\widehat{var(Q_i)}$ and $B = \frac{1}{m-1}\sum_{i=1}^{m}(\widehat{Q_i} - \bar{Q})^2$.

Confidence intervals and p-values will be from a t distribution with degrees of freedom given by:

$$df = (m-1)(1 + \frac{m\bar{U}}{(m+1)B})^2$$

Example Stata code for the missing data sensitivity analysis

```
mkspline age_spline = age, cubic nknots(3) displayknots // creating splines
mkspline haemoglobin_spline = haemoglobin, cubic nknots(3) displayknots
mkspline creatinine_spline  = creatinine, cubic nknots(3) displayknots

local m = 10 // number of imputations

foreach p0 in 0.15 0.2 0.25 0.3 0.35 0.4  { // proportion of events in u.c group
      foreach d1 in -0.1 -0.05 0 0.05 0.1  { // difference in prop between groups
            local p1 = `p0' + `d1' // proportion of events in intervention group
            preserve

*Imputing
            forvalues i = 1 (1) `m' {
                  qui gen _`i'_postopinfec_30 = postopinfec_30
                  forvalues t = 0 (1) 1 {
                        qui{
                        gen miss_order_`i'_`t' = runiform(0,1) ///
                        if treat ==`t' ///
                  & postopinfec_30 ==. // generating random variable to sort on
                        sort miss_order_`i'_`t' // sorting

                        gen miss_no_`i'_`t' =_n if treat ==`t' ///
                        & postopinfec_30 ==.
                        qui count if treat ==`t' & postopinfec_30 ==.

                        replace _`i'_postopinfec_30 = 1 ///
                        if miss_no_`i'_`t' < `p`t''*r(N) ///
                         & treat ==`t' & postopinfec_30 ==.

                        replace _`i'_postopinfec_30 = 0 ///
```

```
                        if miss_no_`i'_`t' >= `p`t''*r(N) ///
                         & treat ==`t' & miss_no_`i'_`t' !=. ///
                         & postopinfec_30 ==.
                        }

                }
        }

*Analysing imputed data sets
        forvalues i = 1 (1) 10 {
                qui melogit _`i'_postopinfec_30  i.treat ///
                        i.plan_surg_proc i.asa_grade ///
                age_spline* haemoglobin_spline* creatinine_spline* ///
                 i.gender || country:, or
                scalar est`i'= _b[1.treat] // storing treatment estimate
                scalar var`i' = (_se[1.treat])^2 // storing standard error
        }


*Combining estimates
        scalar q_bar = (est1 + est2 +est3 + est4 + est5 + est6 + est7 + ///
         est8 + est9 + est10)/`m'

        *Combining variances
        scalar u_bar = (var1 + var2 + var3 + var4 + var5  + var6 + var7 + ///
         var8 + var9 + var10)/`m'

        scalar B = ((est1-q_bar)^2 + (est2-q_bar)^2 + (est3-q_bar)^2 ///
        +(est4-q_bar)^2 +  (est5-q_bar)^2 + (est6-q_bar)^2 + ///
         (est7-q_bar)^2 + (est8-q_bar)^2 + ///
         (est9-q_bar)^2 + (est10-q_bar)^2)/(`m'-1)

        scalar varQ = u_bar+ (1+(1/`m'))*B
        scalar imp_se = varQ^0.5
        di "se: " imp_se

        *Calculating degrees of freedom
        local df = (`m'-1)*(1+(`m'*u_bar/((`m'+1)*B)))^2

        *Calculating p valaue
        local p = 2*(1-t(`df', abs(q_bar/imp_se)))

        *Confidence limits
        local ul = q_bar +  imp_se*invt(`df', 0.975)
        local ll = q_bar - imp_se*invt(`df', 0.975)

        *Displaying results:
        di "Event rate amongst usual care group with missing data: `p0'"
        di "Event rate amongst intervention group with missing data: `p1'"
        di "Estimated odds ratio for treatment effect (95% CI): ///
        " exp(q_bar) " (" exp(`ll') ", " exp(`ul') ")"

        restore
    }
}
```

Appendix 5: Tables

Table 1 - Baseline table

	Complete data		Summary measure	
	Intervention no. (%)	**Usual care no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Age – mean (SD)				
Female - no. (%)				
BMI (kg/m2) – mean (sd)				
Planned surgical procedure – no. (%)				
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 major surgery involving gut resection				
Planned level of care on the first night after surgical procedure – no. (%)				
Critical care level 3				
Critical care level 2				
Post-anaesthesia care unit				
Surgical ward				
ASA score – no. (%)				
II				
III				
IV				
Haemoglobin (g/l) – mean (SD)				
Creatinine (µmol/L) – mean (SD)				
eGFR (ml/min/1.73m^2) – mean (SD)				
Co-morbid disease – no. (%)				
Chronic respiratory disease				
Chronic obstructive pulmonary disease (COPD)				
Asthma				
Interstitial lung disease or pulmonary fibrosis				
Ischaemic heart disease				
Diabetes mellitus				

Heart failure				
Liver cirrhosis				
Active cancer				
If yes – is cancer the indication for surgery?				
Previous stroke or transient ischaemic attack				
Current smoker (within the last 14 days)				
Preoperative immunosuppressant therapy within 30 days before surgery – no. (%)				
None				
Steroids				
Chemotherapy				
Other immunosuppressant				
Positive SARS-COV-2 Test before surgery no. (%)*)				

***)** Variable was not collected from outset and therefore not available for all participants

Table 2 - Clinical management of patients during intervention period

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Characteristics of surgery				
Duration of surgery - median (IQR), min				
Surgical procedure performed – no. (%)				
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 major surgery involving gut resection				
Surgical technique – no. (%)				
Open surgical technique				
Laparoscopic or laparoscopic assisted technique				
Laparoscopic converted to open				
Anaesthetic technique				
General anaesthesia – no. (%)				
Spinal / epidural – no. (%)				
Tracheal tube removed at end of surgery? – no. (%)				
Time spent in post-anaesthesia care unit at end of surgery – median (IQR)				
Level of care on the first night after surgery – no. (%)				
Critical care level 3				
Critical care level 2				
Post-anaesthesia care unit				
Surgical ward				
Fluids – during surgery				
Primary fluid used for volume replacement during surgery – no. (%)				
Balanced' crystalloid				

0.9% sodium chloride				
Gelatin-based colloid				
Starch-based colloid				
Albumin				
None				
Other				
Total volume of intravenous crystalloid during surgery (ml) – mean (SD)				
Total volume of intravenous colloid during surgery (ml) – mean (SD)				
Total volume of red cell and other blood products during surgery (ml) – mean (SD)				
Total volume of all fluids during surgery (ml) – mean (SD)				
Fluids – four hours after surgery				
Primary fluid used for volume replacement after surgery – no. (%)				
Balanced' crystalloid				
0.9% sodium chloride				
Gelatin-based colloid				
Starch-based colloid				
Albumin				
None				
Other				
Total volume of intravenous crystalloid after surgery (ml) – mean (SD)				
Total volume of intravenous colloid after surgery (ml) – mean (SD)				
Total volume of red cell and other blood products after surgery (ml) – mean (SD)				
Total volume of all fluids after surgery (ml) – mean (SD)				
Drugs used during intervention period				
Inotrope infusion used – no. (%)				
Dobutamine				
Dopexamine				
Neither				
Infusion rate reduced due to tachycardia? – no. (%)				

Yes (during surgery)				
Yes (after surgery)				
No				
Infusion site – no. (%)				
Central vein				
Peripheral vein				
Bolus vasopressor or inotrope agent used during intervention period - no. (%)				
Infusion of vasopressor or inotrope (other than dopexamine or dobutamine) used during intervention period - no. (%)				
Additional research staff present to help deliver cardiac output-guided haemodynamic therapy during surgery - no. (%)				
Additional research staff present to help deliver cardiac output-guided haemodynamic therapy in the four hours after surgery - no. (%)				

Table 3 - Main results for analysis of primary and secondary outcomes

	Number included in analysis		**Summary measure**				
	Intervention no. (%)	Usual Care no. (%)	Intervention no. (%)	Usual Care no. (%)	Odds ratio (95% CI)	p-value	Adjusted risk difference (95% CI)
Postoperative infection within 30 days of randomisation (primary outcome)							
Postoperative infection within 30 days of surgery							
Mortality within 180 days of randomisation							
Acute kidney injury within 30 days of randomisation							
Acute cardiac event within 24 hours of randomisation							
Acute cardiac event within 30 days of randomisation							

Table 4 - Results for analysis of process measures

	Number included in analysis		Summary measure			
	Intervention no. (%)	Usual Care no. (%)	Intervention	Usual Care	Odds ratio (95% CI)	p-value
Duration of post-surgical hospital stay for survivors – median (IQR)						
Survived to hospital discharge – no. %	n/a	n/a			n/a	n/a
Died in hospital – no. %	n/a	n/a			n/a	n/a
Number of critical care free days up to 30 days from randomisation – mean (SD)						

Table 5 - Results for subgroup analysis of primary outcome

	Number included in analysis		**Postoperative infection within 30 days of randomisation**			
Planned surgical procedure	Intervention no. (%)	Usual Care no. (%)	Intervention no. (%)	Usual Care no. (%)	Odds ratio (95% CI)	p-value for interaction
Resection of colon, rectum or small bowel						
Resection of pancreas and bowel						n/a
Resection of stomach (non-obesity surgery)						n/a
Resection of oesophagus (non-obesity surgery)						n/a
Obesity surgery						n/a
Other major surgery involving gut resection						n/a

Table 6 - Results of sensitivity analysis for mortality acting as a competing risk for postoperative infection with 30 days of randomisation

	Number included in analysis		**Summary measure**			
	Intervention no. (%)	Usual Care no. (%)	Intervention	Usual Care	Sub-hazard ratio (95% CI)	p-value
Time to postoperative infection within 30 days of randomisation - median (IQR)						
Postoperative infection within 30 days – no. (%)	n/a	n/a			n/a	n/a
Died before day 30 without experiencing a postoperative infection –no. (%)	n/a	n/a			n/a	n/a

Table 7 – Estimates of effect of treatment in patients who underwent surgery

		Numbers included in analysis		**Number who received surgery**		
	Mean of prior for difference between usual care and no surgery.	Intervention no. (%)	Usual Care no. (%)	Intervention no. (%)	Usual Care no. (%)	Difference in percentage points (95% CI*)
Postoperative infection within 30 days of randomisation (primary outcome)	Main					
	Sensitivity 1 (lower)					
	Sensitivity 2 (higher)					
	ITT analysis	n/a	n/a	n/a	n/a	
Acute cardiac event within 24 hours of randomisation	Main					
	Sensitivity 1 (higher 1)					
	Sensitivity 2 (higher 2)					
	ITT analysis	n/a	n/a	n/a	n/a	
Acute cardiac event within 30 days of randomisation	Main					
	Sensitivity 1 (lower)					
	Sensitivity 2 (higher)					
	ITT analysis	n/a	n/a	n/a	n/a	

*For Bayesian analysis 95% credible intervals are given. For intention to treat analysis, we present a 95% confidence interval.

Table 8 - Results of sensitivity analysis for data being missing not at random of postoperative infection within 30 days of randomisation

Proportion with missing data in Usual care assumed to have event	Proportion with missing data in intervention group assumed to have event	Odds ratio (95% CI)
0.15	0.05	
	0.1	
	0.15	
	0.2	
	0.25	
0.2	0.1	
	0.15	
	0.2	
	0.25	
	0.3	
0.25	0.15	
	0.2	
	0.25	
	0.3	
	0.35	
0.3	0.2	
	0.25	
	0.3	
	0.35	
	0.4	
0.35	0.25	
	0.3	
	0.35	
	0.4	
	0.45	
0.4	0.3	
	0.35	
	0.4	
	0.45	
	0.50	

Table 9 – Components of primary outcome - postoperative infections within 30 days of randomisation

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Surgical site infection (superficial)				
Surgical site infection (deep)				
Surgical site infection (organ space)				
Pneumonia				
Infection, Source uncertain				
Laboratory confirmed blood stream infection				

Table 10 - Components of acute cardiac events within 24hrs of randomisation

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Arrhythmia				
Myocardial infarction				
Myocardial injury after non-cardiac surgery				
Cardiac arrest with successful resuscitation				
Cardiogenic pulmonary oedema				

Table 11 - Components of acute within 30 days of randomisation

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Arrhythmia – no. (%)				
Myocardial infarction – no. (%)				
Myocardial injury after non-cardiac surgery – no. (%)				
Cardiac arrest with successful resuscitation – no. (%)				
Cardiogenic pulmonary oedema – no. (%)				

Table 12 - Other postoperative complications

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Acute psychosis or delirium – no. (%)				
Acute Respiratory Distress Syndrome – no. (%)				
Anaphylaxis – no. (%)				
Anastomotic breakdown – no. (%)				
Bowel infarction – no. (%)				
Gastro-intestinal bleed – no. (%)				
Multi-organ dysfunction syndrome – no. (%)				
Paralytic ileus – no. (%)				
Perforated viscus (e.g. bowel, gall bladder etc) – no. (%)				
Other postoperative haemorrhage (not GI bleed) – no. (%)				
Pulmonary embolism – no. (%)				
Stroke – no. (%)				
Respiratory failure associated with SARS-Cov-2*) – no. (%)				
Other complication associated with SARS-Cov-2*) – no. (%)				
Other – no. (%)				

*) Variable was not collected from outset and therefore not available for all participants

Table 13 - Additional treatments

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Critical care admission to treat complication – no. (%)				
Invasive mechanical ventilation after leaving the operating room – no. (%)				

Table 14 - Self assessment of blinding for outcome assessment

	Complete data		Summary measure	
	Intervention – no. (%)	**Usual care – no. (%)**	**Intervention (n=…)**	**Usual care (n=…)**
Assessor suitably blinded				
Assessor may have known allocation				
Assessor knew allocation				

Table 15 - Serious adverse events related to the Optimise II trial procedures

	Summary measure	
	Intervention (n=…)	**Usual care (n=…)**
Number of serious adverse events		
Number of patients experiencing one or more serious adverse events		

Table 16 - Protocol deviations

	Intervention (n=…)	**Usual care – (n=…)**
Patients with at least one protocol deviation		
Did not receive cardiac output monitoring (intervention group)		n/a
Did not receive inotrope (intervention group)		n/a
Received incorrect dose of inotrope (intervention group)		n/a
Received cardiac output monitoring (usual care group)	n/a	

Table 17- Reasons for protocol deviations

	Intervention	Usual care
Did not receive cardiac output monitoring (intervention group)		
Clinician decision		n/a
Equipment related		n/a
Communication error		n/a
Other		n/a
Did not receive inotrope (intervention group)		
Clinician decision		n/a
Equipment related		n/a
Communication error		n/a
Other		n/a
Received incorrect dose of inotrope (intervention group		
Clinician decision		n/a
Equipment related		n/a
Communication error		n/a
Other		n/a
Received cardiac output monitoring (usual care group)		
Clinician decision	n/a	
Equipment related	n/a	
Communication error	n/a	
Other	n/a	