Enhanced Peri-Operative Care for High-risk patients (EPOCH) Trial

Statistical Analysis Plan

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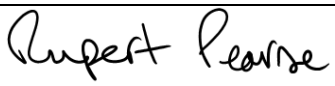
Signature	
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1. INTRODUCTION

Purpose of statistical analysis plan

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 EPOCH trial. Subsequent papers of a more exploratory nature will not be bound by this strategy but will be expected to follow the broad principles laid down within it. Any exploratory, post-hoc or unplanned analyses will be clearly identified as such in the respective study analysis report.

This document has been developed prior to examination of unblinded trial data. This plan is intended not to change or contradict the general aims of the protocol, but rather expand on them. In the event of a discrepancy the analyses described here will supersede those in earlier documents.

Background

EPOCH is a stepped wedge, cluster randomised trial which aims to evaluate the effect of a quality improvement intervention to promote the implementation of an integrated peri-operative care pathway in patients undergoing emergency laparotomy. The trial will take place in 90 hospitals, which have been grouped into 15 clusters based on geographical location (with approximately 6 hospitals per cluster). The trial will take place over an 85 week period, which has been divided into 17 time periods of 5 week each. All hospitals will start out receiving usual care during the first time period; during each subsequent time period, one cluster will switch over to the quality improvement intervention (the order the clusters switch has been randomised). By time period 16, all clusters will be receiving the quality improvement intervention.

Inclusions/exclusion criteria

Inclusion criteria

- Included on the NELA database
- Age 40 years and over
- Undergoing non-elective surgery
- Undergoing open abdominal surgery
- Admitted to hospital during the 85 week trial period from March 3rd 2014, to Oct 19th, 2015

Exclusion criteria

- Patients who have previously been included in the EPOCH trial
- Laparotomy to treat complications of recent elective surgery
- Simple appendicectomy
- Gynaecological laparotomy
- Surgery related to organ transplant
- Laparotomy for traumatic injury

Changes from protocol

- Defined the process measures to be summarised
- Defined which baseline risk factors were to be adjusted for in the analysis
- Clarified that hospitals which discontinue their emergency laparotomy service, or which merge with another hospital during the trial period will be excluded from the analysis at the point of discontinuation or merger
- Clarified that the analysis will include a random-effect for the hospital-time period interaction. This is in accordance with new research indicating this analysis approach is required to preserve type I error rates at their nominal level
- Clarified that hospital re-admission will be analysed using a competing-risk time-to-event model rather than a logistic regression model
- Clarified that time to hospital discharge will be analysed using a competing-risk time-to event model rather than a simple time-to-event model

Note that all changes from the protocol were made before any investigators had access to any trial data or to any results.

Changes from SAP version 1.0

- Changed the covariates to be adjusted for in the analysis of clinical outcomes from age and gender, to age, gender, and indication for surgery.

Note that all changes from version 1.0 of the SAP were made before any investigators had access to any clinical outcome data.

Changes from SAP version 2.0

- We had planned to calculate the primary outcome (mortality within 90 days of surgery) based on data obtained from government registries (i.e. Office for National Statistics in England, and similar agencies in Scotland and Wales), and analyse it as a binary endpoint using a logistic regression model. However, due to unforeseen issues, we were unable to obtain data from the Welsh registry (but did obtain data from the English and Scottish registries). This meant that under our original definition, all patients in Wales would be excluded from the analysis due to missing data, which could adversely affect results. In order to avoid excluding patients from Wales from the primary outcome analysis, we opted to change the analysis approach from a logistic regression model based on a binary endpoint to a survival analysis model based on a time-to-event endpoint; this allowed us to calculate time-to-mortality for patients in Wales

based on in-hospital mortality data which is collected as part of NELA (with patients being censored at the time of hospital discharge). Time-to-mortality will still be calculated based on government registry data for patients in England and Scotland. We changed the secondary outcome 'mortality within 180 days' in the same manner. The updated method for deriving these outcomes is available in Appendix 3.

- One of the sensitivity analyses regarding missing data for the primary outcome was based upon a binary endpoint; this has been removed, as this approach does not work well for time-to-event outcomes.
- Removed sensitivity analysis for primary outcome which included patients who presented to a hospital which merged with other hospitals after the date of the merge, as this affected very few patients.
- Added specification that missing data in the baseline covariates that will be adjusted for in the analysis will be handled using mean imputation (for continuous variables) and a missing indicator variable (for categorical variables).
- Appendix 5: Updated to reflect new data fields in NELA, and a 'multiple indications' category was added as the categories are not mutually exclusive.
- Clarified that the additional analysis assessing the intervention in patients aged <40, or who underwent laparoscopic surgery would not be a formal analysis, but would only present summary statistics. This is because we expect few patients and outcome events in this group, and our specified statistical models (with three levels of random-effects) would likely not work well.
- Appendix 2: clarified that patients who presented to a hospital that merged with other hospitals after the date of the merge would be excluded from the analysis (this was stated in v2.0 of the SAP, but inadvertently left out from the appendix)

Changes from version 2.0 of the SAP were after the trial statistician (BK) had access to data, but before statistical analysis began (i.e. during the data cleaning stage), and before any other investigators had access to the data.

2. OUTCOME MEASURES

Primary outcome

- All-cause mortality within 90 days following surgery

Secondary outcomes

- All-cause mortality within 180 days following surgery
- Duration of hospital stay (defined as the number of days from surgery until hospital discharge)
- Hospital re-admission within 180 days of surgery

The start of surgery will be defined as when the patient enters the operating theatre or anaesthetic room.

Process measures

1. Consultant led decision to operate
2. When consultant led decision to operate, did this consultant personally review patient at time of decision?
3. Preoperative documentation of risk
4. Time from decision made to operate to entry into operating theatre
5. Patient entered operating theatre within time-frame specified based on their urgency level (i.e. <2 hours, 2-6 hours, 6-18 hours, or >18 hours)
6. Consultant surgeon present in operating theatre
7. Consultant anaesthetist present in operating theatre
8. Goal directed fluid therapy used during surgery
9. Arterial lactate measured at end of surgery
10. Critical care admission immediately after surgery

3. STUDY METHODS

Overall study design and plan

Multi-centre, stepped wedge cluster randomised trial conducted in 90 NHS hospitals over an 85 week period, divided into 17 time period of 5 weeks. Hospitals will be grouped into fifteen clusters of six on a geographical basis. The quality improvement intervention will commence in one geographical area each five week step from the 2nd to the 16th time period, with the order of geographical areas determined by computer based randomisation.

Randomisation

Simple randomisation was used to randomise one geographical area of hospitals to receive the intervention in each of the fifteen time periods 2 to 16. Randomisation was performed by an independent statistician. Local investigators were notified 12 weeks in advance of activation of the quality improvement project at their hospital.

Sample size

Prospectively collected data from the recently published Emergency Laparotomy Network study in 35 NHS hospitals closely match our inclusion/exclusion criteria and describe a median of 184 eligible patients aged ≥40 years per hospital per year (range 32-736). Data from the Hospital Episodes Statistics database for the year ending April 2011 gives average 90-day mortality as 25%. These data have been used to estimate the baseline mortality rate and between hospital coefficient of variation. Power calculations are based on the methodology proposed by Hussey & Hughes, for an analysis with fixed time effects and random cluster effects, modified to exclude data collected during the five week period in which the intervention commences in individual hospitals. The trial will be conducted in at least 90 NHS hospitals over a period of 85 weeks during which time we expect to receive data describing 27,540 patients undergoing emergency laparotomy. For a baseline 90-day mortality of 25%, between hospital coefficient of variation of 0.15, constant case-load (18 patients per 5 weeks per hospital) and assuming independent hospital effects, the study would achieve 92% power to detect a 12% relative risk reduction in mortality from 25% to 22% (two-sided $p<0.05$). This calculation is insensitive to the coefficient of variation but sensitive to the effect size. In practice, power may be reduced by correlation between hospitals within geographic areas and by variation in case-load between hospitals. The worst case scenario is one where each of the 15 geographic areas functions effectively as a single large hospital, reducing the power to 83%. This figure incorporates an adjustment for variable case-load from the pilot data. Thus the power of the study to detect a 12% relative risk reduction lies between 83% and 92%.

4. DATA COLLECTION

Data to be collected at different stages:
Pre-operative data: Age, Sex, American Society of Anesthesiologists (ASA) Score, Co-morbid disease, Date of hospital admission, Admitting specialty, Time and date of decision to perform surgery, Time to diagnostic imaging (usually computed tomography scan of the abdomen), Documented mortality risk before surgery (Y/N).

Intra-operative data: Urgency of surgery, Duration, time and date of surgery, Grades of most senior surgeon and anaesthetist present in theatre, Surgical procedure performed, Underlying pathology.

180-day follow-up: Critical care admission, Duration of hospital stay, Hospital readmission and mortality.

5. ANALYSIS PRINCIPLES

Patients and hospitals to be included in the analysis

All analyses will be conducted on an intention-to-treat basis. All eligible patients with available outcome data who attended a participating hospital during the 85-week trial period will be included in the analysis. Patients who presented to hospital during the 5-week time period immediately after the quality improvement implementation will be excluded from the analysis, in order to allow time for the intervention to take effect.

Hospitals that underwent randomisation but subsequently withdrew prior to the trial start date (March 3rd, 2014) will be excluded from the analysis. Hospitals that withdraw from the trial during the trial period or do not implement the intervention will be included in the analysis. Hospitals that discontinue their emergency laparotomy service during the trial period will be included in the analysis up until the point of discontinuation, and excluded after this point. Hospitals that merge with another hospital(s) during the trial period will be included in the analysis up until the point of the merger, and excluded after this point. Hospitals that withdraw from data collection during the trial period will be included in the analysis up until the point of the withdrawal, and excluded after this point. Patients will be considered exposed to the intervention based on the randomisation schedule, regardless of whether the intervention was actually implemented.

Justification for excluding hospitals who merge with other hospitals during the trial period

When hospitals merge they can be seen to form a 'new' hospital. The types of patients who present to the new hospital may be different to those that presented to the 'original' hospital (e.g. due to a wider or different catchment area). There may be differences in staff between the new and original hospitals (e.g. differences in doctors, surgeons, nurses, etc). In some cases there may be differences in available equipment. This could all lead to substantial differences between the pre- and post-merger outcomes for patients. Because the stepped-wedge trial relies heavily on a within-hospital comparison, differences between pre- and post-merger outcomes could substantially skew this comparison, which could lead to bias in the estimated treatment effect.

General analysis principles

For analysis of the primary and secondary outcomes, the following summaries will be provided:

- The number of patients included in the analysis, by treatment group
- The number of hospitals included in the analysis
- A summary statistic for the outcome (e.g. the number (%) of patients experiencing an event for binary outcomes)
- The estimated treatment effect with its 95% confidence interval and a two-sided p-value

The significance level is set at 5%. All analyses will include time-period in the model as a fixed-effect using indicator variables. All analyses will adjust for age, gender, and indication for surgery (peritonitis, perforation, abdominal infection, intestinal obstruction, haemorrhage, ischaemia, other, or multiple indications) using fixed factors. Age will be included as a continuous covariate, and will be assumed to have a linear association with the outcome. Missing baseline data will be imputed using mean imputation for continuous variables (age), and using a missing indicator for categorical variables (gender, indication for surgery) (based on guidance from White IR, Thompsons SG. *Adjusting for partially missing baseline measurements in randomized trials*. Stat Med 2005).

Primary outcome

The primary outcome (all-cause mortality up to 90 days following surgery) will be analysed using a mixed-effects parametric survival model, with a Weibull survival distribution. This model will include random-intercepts for geographical area, hospital, and the interaction between hospital and time-period. Time-period will be included in the model as a fixed-effect using indicator variables. Age, gender, and indication for surgery will also be included in the model as fixed factors.

Note that we are including the interaction between hospital and time-period as a random-effect as recent research has indicated this is required in order to preserve type I error rates at the nominal level (i.e. Morgan K, Forbes A, Keogh R, Jairath V, Kahan B. *Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome*. Accepted.)

An example dummy dataset is provided in table 1 and example Stata code is provided below to demonstrate how this analysis will be implemented.

Example Stata code

```
stset time_to_outcome, failure(outcome)

mestreg treatment i.time_period age gender i.indication_surgery || geo_area: || hospital: ||
hospital_time_period: , distribution(weibull)
```

If there are convergence issues with this analysis approach, we will use the strategy shown in table 2 to find an analysis approach which converges.

Table 1 – Example dataset

Geographical area	Hospital	Time period	Hospital*time period interaction	Treatment	Patient
1	1	1	1	0	1
1	1	1	1	0	2
1	1	2	2	0	3
1	1	2	2	0	4
1	2	1	3	0	5
1	2	1	3	0	6
1	2	2	4	0	7
1	2	2	4	0	8
2	3	1	5	0	9
2	3	1	5	0	10
2	3	2	6	1	11
2	3	2	6	1	12
2	4	1	7	0	13
2	4	1	7	0	14
2	4	2	8	1	15
2	4	2	8	1	16

Table 2 – Analysis approaches to be used if the primary method of analysis fails to reach convergence

	Change from previous strategy	**Example Stata code**
1	Remove the random-effect for the hospital/time-period interaction	*mestreg outcome treatment i.time_period age gender i.indication_surgery || geo_area: || hospital: , distribution(weibull)*
2	Remove the random-effect for hospital	*mestreg outcome treatment i.time_period age gender i.indication_surgery || geo_area: , distribution(weibull)*
3	Adjust for the fixed-effect of time as a continuous covariate using restricted cubic splines with 7 knot points (where rcs_time_period* are the variables forming the restricted cubic spline)	*mestreg outcome treatment rcs_time_period* age gender i.indication_surgery || geo_area: , distribution(weibull)*

Secondary outcomes

All-cause mortality up to 180 days

All-cause mortality up to 180 days following surgery and hospital re-admission within 180 days of surgery will be analysed using the same approach as the primary outcome.

Duration of hospital stay

Duration of hospital stay will be analysed using a competing-risk time-to-event model, which recognises mortality as a competing risk for hospital discharge. 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 geographical area. This analysis will be implemented in Stata as follows:

stset cc_time_to_discharge, failure(cc_discharge == 1)
stcrreg treatment i.time_period age gender i.indication_surgery, compete(cc_discharge == 2) vce(cluster geo_area)

Where:
cc_discharge is a variable indicating whether the patient was discharged home (=1), died in hospital (=2), or was censored (=0), and *cc_time_to_discharge* is a variable indicating the time to the event.

Hospital re-admission within 180 days

This outcome will be analysed using a competing-risk time-to-event model, which recognizes mortality as a competing risk for hospital re-admission. It will be implemented using the same code as *duration of hospital stay* above.

Secondary analyses of the primary outcome

Evaluating the effect of the intervention over time

We will perform a secondary analysis of the primary outcome to evaluate the effect of the intervention over time (i.e. whether the intervention effect improves over time). This analysis will include patients who presented to hospital during the 5-week period immediately after implementation of the quality improvement intervention. We will evaluate the following four groups:

- Usual care;
- The quality improvement (QI) intervention implemented for less than 5 weeks
- The QI intervention was implemented for 5 weeks or more and less than 10 weeks
- The QI intervention was implemented for 10 weeks or more

This analysis will allow us to determine whether the effectiveness of the QI intervention improves over time. The analysis will be implemented using the same method as for the primary analysis of the primary outcome.

Inclusion of other patient populations which may be affected by the intervention

We will perform a sensitivity analysis to assess whether results are generalisable to other patient populations which may have been affected by the intervention. This includes patients who underwent laparoscopic surgery, and patients who are aged 18-40 years.

Due to the small number of patients in these groups, we will summarise results descriptively, rather than undertaking a formal statistical analysis. We will summarise the number (%) of patients in the treatment arms who experience a primary outcome event. The denominator for this analysis will include patients who either underwent laparoscopic surgery or were aged 18-40 years (or both), and who met all other eligibility criteria.

Process measures

The process measures will be summarized according to treatment group. For example, for binary process measures (e.g. 'Goal directed fluid therapy used during surgery'), the number (%) of patients for whom the measure was met will be summarised separately for patients presenting during the usual care period and patients presenting during the intervention period.

Because the trial intervention is complex, and we will not be able to distinguish the effects of a change in any one process measure on patient outcomes, no formal statistical analysis will be performed. This is to avoid any misinterpretation that changes in some process measures affected patient outcomes whilst others did not.

Graphs and other data summaries

Survival curves for mortality up to 180 days from surgery

We will present two graphs which display the survival curves for mortality up to 180 days after surgery. Survival curves will be presented for each treatment arm. The first graph will be a Kaplan-Meier plot. It should be noted that this plot is affected by overall time trends in the outcome (e.g. if mortality rates improved over time, regardless of the intervention).

Therefore, the second graph will show the estimated survival curve based on a mixed-effects time-to-event model, which corrects for time trends. The Stata code to implement this graph is:

```
stset time_to_death, failure(died_180days)
mestreg treatment i.time_period age gender i.indication_surgery || geo_area: || hospital: ||
hospital_time_period: , distribution(Weibull)

stcurve, surv at1(treatment=0) at2(treatment=1)
```

Other data summaries

- The number of patients who are excluded from each analysis (and the reasons why) will be summarized.
- The number of cluster activation meetings that occurred within ±2 weeks of the date based on the randomisation list
- The number of hospitals sending at least one person to the first QI activation meeting
- The number of hospitals sending at least one of their named QI leads to the first QI activation meeting
- The number of hospitals sending at least one person to the second QI activation meeting
- The number of hospitals sending at least one of their named QI leads to the second QI activation meeting

Appendix 1: Dummy tables

Table 1 – Patient characteristics

	Missing data		Summary measure	
	Intervention – no. (%)	**Control – no. (%)**	**Intervention (n=...)**	**Control (n=...)**
Baseline characteristics				
Female – no. (%)				
Age – mean (SD)				
Indication for surgery – no. (%)				
Peritonitis				
Perforation				
Abdominal infection				
Intestinal obstruction				
Haemorrhage				
Ischaemia				
Other				
Pre-operative characteristics				
Estimated risk of death – no. (%)				
Low (<5%)				
Medium (5-10%)				
High (>10%)				
Not documented				
ASA score – no. (%)				
1 (no systemic disease)				
2 (mild systemic disease)				
3 (severe systemic disease, not life threatening)				
4 (severe, life threatening)				
5 (moribund patient)				
P-POSSUM score – mean (SD)				
Blood lactate (mmol/l) – mean (SD)				
Systolic blood pressure (mmHg) – mean (SD)				
Glasgow coma scale – mean (SD)				

Table 2 – Main results for primary and secondary outcomes

	Missing data (intervention)	Missing data (control)	Summary measure (intervention)	Summary measure (control)	Treatment effect (95% CI)	P-value
All-cause mortality up to 90 days from surgery (primary outcome)						
All-cause mortality up to 180 days from surgery						
Hospital re-admission within 180 days of surgery						
Duration of hospital stay						

Table 3 – Process measures

	Missing data (intervention)	Missing data (control)	Summary measure (intervention)	Summary measure (control)
Consultant led decision to operate				
When consultant led decision to operate, did this consultant personally review patient at time of decision?				
Preoperative documentation of risk				
Time from decision made to operate to entry into operating theatre				
Patient entered operating theatre within time-frame specified based on their urgency level (i.e. <2 hours, 2-6 hours, 6-18 hours, or >18 hours)				
Consultant surgeon present in operating theatre				
Consultant anaesthetist present in operating theatre				
Goal directed fluid therapy used during surgery				
Arterial lactate measured at end of surgery				
Critical care admission immediately after surgery				

Appendix 2: Determining eligibility criteria in NELA dataset

Inclusions/exclusion criteria

Inclusion criteria

- Included on the NELA database
- Age 40 years and over
- Undergoing non-elective surgery
- Undergoing open abdominal surgery
- Admitted to hospital during the 85 week trial period from March 3rd 2014, to Oct 19th, 2015

Exclusion criteria

- Data previously included in the EPOCH trial
- Laparotomy to treat complications of recent elective surgery
- Simple appendicectomy
- Gynaecological laparotomy
- Surgery related to organ transplant
- Laparotomy for traumatic injury

Identifying eligible patients from the NELA dataset

Inclusion criteria	NELA field ID	NELA Data item	Possible values	Patient included if NELA data item:
Age 40 years and over	1.4	Age on arrival	Any age	≥40
Undergoing non-elective surgery				Elective surgery cases not collected by NELA
Undergoing open abdominal surgery	5.4	Procedure approach	-Open -Laparoscopic -Laparoscopic converted to open -Laparoscopic assisted	Open, Laparoscopic converted to open, or Laparoscopic assisted
Admitted within 85 week period from March 3rd, 2014 to Oct 19th, 2015	1.9	Date and time patient admitted to this hospital	Any date	From March 3rd 2014 to Oct 19th, 2015 (inclusive)

Identifying ineligible patients from the NELA dataset

Exclusion criteria	NELA field ID	NELA Data item	Possible values	Patient excluded if NELA data item:
Laparotomy to treat complications of recent elective surgery	5.1	Type for procedure	-First surgical procedure after admission -Surgery for complication of previous surgical procedure within same admission	Surgery for complication of previous surgical procedure within same admission
	5.2	Indication for surgery	-Planned relook -Peritonitis -Perforation -Abdominal abscess -Anastomotic leak -Intestinal fistula -Sepsis (other) -Intestinal obstruction -Haemorrhage -Ischaemia -Colitis -Abdominal wound dehiscence -Abdominal compartment syndrome	Planned relook

			-Other	
Simple appendicectomy				Not collected by NELA
Gynaecological laparotomy				Not collected by NELA
Surgery related to organ transplant				Not collected by NELA
Laparotomy for traumatic injury				Not collected by NELA

Patients included in the main analyses for the primary, secondary, and process measure outcomes

The following algorithm will be used to determine which patients will be included in the main analysis for each outcome. Briefly, eligible patients who are recorded on the NELA database, who have not presented to hospital in the 5 week period immediately after implementation of the intervention, and who have available outcome data will be included in the analysis.

Algorithm:

Patients will be included if:

- 1.4 ≥ 40; *and*
- 5.4 = Open, Laparoscopic converted to open, or Laparoscopic assisted; *and*
- 1.9 is between March 3rd 2014 and October 19th 2015 (inclusive); *and*
- 1.9 is not between the date of implementation (based on the randomisation list) and 35 days after the implementation date; *and*
- 5.1 ≠ Surgery for complication of previous surgical procedure within same admission; *and*
- 5.2 ≠ Planned relook; *and*
- Patient has not presented to a hospital that has merged with other hospitals *after* the date of the merge; *and*
- Outcome variable is not missing

If any of the above data fields for the eligibility criteria are missing, the patient will be excluded from analysis.

Evaluating the effect of the intervention over time

This analysis will include the same set of patients as in the primary analyses above, but will additionally include patients who presented during the 5-week period immediately after implementation, i.e. the algorithm will be the same as above, except the criteria *"1.9 is not between the date of implementation (based on the randomisation list) and 35 days after the implementation date"* will be removed.

Inclusion of other patient populations which may be affected by the intervention

Patients will be included if:

- 1.4 < 40 *or* 5.4 = Laparoscopic; *and*
- 1.9 is between March 3rd 2014 and October 19th 2015 (inclusive); *and*
- 1.9 is not between the date of implementation (based on the randomisation list) and 35 days after the implementation date; *and*
- 5.1 ≠ Surgery for complication of previous surgical procedure within same admission; *and*
- 5.2 ≠ Planned relook; *and*
- Outcome variable is not missing

Appendix 3: Calculating primary and secondary outcomes

All primary and secondary outcomes will be measured from the date of surgery. The date of surgery is based on question 4.1 in the NELA dataset *"Date and time of entry in to operating theatre/anaesthetic room (not theatre suite)"*.

Outcome	Calculation
All-cause mortality within 90 days following surgery	This outcome will be defined by two variables: death (yes/no), and the time to death. ***For patients in England and Scotland (using government registry death data):*** *Death:* -'Yes' if the patient died, and the difference between their date of death and 4.1 is less than or equal to 90 -'No' if the patient died, but the difference between their date of death and 4.1 is greater than 90 -'No' if the patient did not die -Missing if the patient died, but their date of death is not available, or if it is unknown whether the patient died, if 4.1 is missing, or if the date of death is before 4.1 and this discrepancy cannot be resolved *Time to death:* -If 'death'='yes', then time to death is calculated as the difference between their date of death and 4.1. If this is 0 (i.e. the patient died on the day of surgery), this will be set to 0.5 days; this is so the patient can be included in the analysis (as Stata excludes outcomes with an event time of 0) -if 'death'='no', this is set to 90 days ***For patients in Wales:*** -'Yes' if 7.7 = "Dead"; and the difference between their date of death (in 7.8) and 4.1 is less than or equal to 90

	-'No' if the patient died, but the difference between their date of death and 4.1 is greater than 90 -'No' if the patient was discharged or still in hospital at day 60 (as patients who are still in hospital at day 60 are sometimes censored at that point in the NELA dataset) -Missing if the patient died, but their date of death is not available, or if it is unknown whether the patient died, if 4.1 is missing, or if the date of death is before 4.1 and this discrepancy cannot be resolved *Time to death:* -If 'death'='yes', then time to death is calculated as the difference between their date of death and 4.1. If this is 0 (i.e. the patient died on the day of surgery), this will be set to 0.5 days; this is so the patient can be included in the analysis (as Stata excludes outcomes with an event time of 0) -if 'death'='no' (i.e. the patient was discharged or the patient is still in hospital at day 60), this is the date of discharge or 90 days (whichever is sooner), or 60 days if they are still in hospital then
All-cause mortality within 180 days following surgery	This outcome will be defined by two variables: death (yes/no), and the time to death. ***For patients in England and Scotland (using government registry death data):*** *Death:* -'Yes' if the patient died, and the difference between their date of death and 4.1 is less than or equal to 180 -'No' if the patient died, but the difference between their date of death and 4.1 is greater than 180 -'No' if the patient did not die -Missing if the patient died, but their date of death is not available, or if it is

	unknown whether the patient died, if 4.1 is missing, or if the date of death is before 4.1 and this discrepancy cannot be resolved *Time to death:* -If 'death'='yes', then time to death is calculated as the difference between their date of death and 4.1. If this is 0 (i.e. the patient died on the day of surgery), this will be set to 0.5 days; this is so the patient can be included in the analysis (as Stata excludes outcomes with an event time of 0) -if 'death'='no', this is set to 180 days ***For patients in Wales:*** -'Yes' if 7.7 = "Dead"; and the difference between their date of death (in 7.8) and 4.1 is less than or equal to 180 -'No' if the patient died, but the difference between their date of death and 4.1 is greater than 180 -'No' if the patient was discharged or still in hospital at day 60 -Missing if the patient died, but their date of death is not available, or if it is unknown whether the patient died, if 4.1 is missing, or if the date of death is before 4.1 and this discrepancy cannot be resolved *Time to death:* -If 'death'='yes', then time to death is calculated as the difference between their date of death and 4.1. If this is 0 (i.e. the patient died on the day of surgery), this will be set to 0.5 days; this is so the patient can be included in the analysis (as Stata excludes outcomes with an event time of 0) -if 'death'='no' (i.e. the patient was discharged or the patient is still in hospital at day 60), this is the date of discharge or 180 days (whichever is sooner), or 60 days if they are still in hospital then
Duration of hospital stay (defined as the number of days from surgery until hospital discharge)	This outcome will be defined by two variables: the discharge event (discharged/died before discharge/censored), and time to the discharge event.

	-*Discharge event* = *'Discharged'* if 7.7 = "Alive"; *time to discharge event* is calculated as difference as the difference in dates between 7.8 and 4.1 --*Discharge event* = *'Died before discharge'* if 7.7 = "Dead"; *time to discharge* is calculated as difference as the difference between the date of death and 4.1 -*Discharge event* = *'Censored'* if 7.7 = "Still in hospital at 60 days"; *time to discharge* is 60 days -Missing if 7.7 = "Alive" and 7.8 is missing or 4.1 is missing, or if 7.7 = "Dead" and a date of death is not available or 4.1 is missing
Hospital re-admission within 180 days of surgery	This outcome will be defined by two variables: the re-admission event (re-admitted/died before re-admission/not re-admitted), and time to the re-admission event. -*Re-admission event* = *'Yes'* if the patient was re-admitted to hospital within 180 days; *time to re-admission event* is calculated as the difference between the date of their first re-admission and 4.1 -*Re-admission event* = *'Died before re-admission'* if the patient died within 180 days and was not re-admitted to hospital; *time to re-admission event* is calculated as difference as the difference between the date of death and 4.1 -*Re-admission event* = *'Censored'* if the patient was alive up to 180 days and not re-admitted to hospital; *time to re-admission event* is 180 -Missing if the patient was re-admitted but their date of re-admission is not available or 4.1 is missing, or if it is unknown whether the patient was re-admitted, or if 7.7 = "Dead" and a date of death is not available or if 4.1 is missing

Appendix 4: Calculating process measures

1. Consultant led decision to operate
2. When consultant led decision to operate, did this consultant personally review patient at time of decision?
3. Preoperative documentation of risk
4. Time from decision made to operate to entry into operating theatre
5. Patient entered operating theatre within time-frame specified based on their urgency level (i.e. <2 hours, 2-6 hours, 6-18 hours, or >18 hours)
6. Consultant surgeon present in operating theatre
7. Consultant anaesthetist present in operating theatre
8. Goal directed fluid therapy used during surgery
9. Arterial lactate measured at end of surgery
10. Critical care admission immediately after surgery

Process measure	**Calculation**
1. Consultant led decision to operate	-'Yes' if 2.4 = "Consultant" -'No' if 2.4 is anything other than "Consultant" -Missing if 2.4 is missing
2. When consultant led decision to operate, did this consultant personally review patient at time of decision?	-'Yes' if 2.5 = "Yes" -'No' if 2.5 = "No" -Missing if 2.5 = "Unknown" *Note: patients for whom 2.4 is not "Consultant" are excluded.
3. Preoperative documentation of risk	-'Yes' if 3.1 = "low (<5%)" or "medium (5-10%)" or "high (>10%)" -'No' if 3.1 = "Not documented" -Missing if 3.1 is missing
4. Time from decision made to operate to entry into operating theatre	-calculated as the difference between date/time in 4.1 and the date/time in 2.2

	-missing if either 2.2 or 4.1 are missing/not known
5. Patient entered operating theatre within time-frame specified based on their urgency level (i.e. <2 hours, 2-6 hours, 6-18 hours, or >18 hours)	-'Yes' if (4) is less than or equal to time specified in 3.22 -'No' if (4) is more than time specified in 3.22 Missing if (4) or 3.22 is missing
6. Consultant surgeon present in operating theatre	-'Yes' if 4.2 = "Consultant" -'No' if 4.2 is anything other than "Consultant" -Missing if 4.2 is missing
7. Consultant anaesthetist present in operating theatre	-'Yes' if 4.3 = "Consultant" -'No' if 4.3 is anything other than "Consultant" -Missing if 4.3 is missing
8. Goal directed fluid therapy used during surgery	-'Yes' if 4.4 = "Cardiac output monitor" or "Other" -'No' if 4.4 = "Not provided" -Missing if 4.4 is missing
9. Arterial lactate measured at end of surgery	-'Yes' if 6.3 = any number -'No' if 6.3 = "Not performed" -Missing if 6.3 is missing
10. Critical care admission immediately after surgery	-'Yes' if 6.24 = "Level 2 HDU" or "Level 3 ICU" -'No' if 6.24 = "Ward" -Missing if 6.24 is missing *Note: patients for whom 6.24 = "Died prior to discharge from theatre complex" will be excluded from the denominator

Appendix 5: Calculating indication for surgery

The variable 'indication for surgery' (which will be included in the regression models for the clinical outcomes) will be derived as in the following table:

Indication for surgery category	Calculation
Peritonitis	-if 5.2 = "Peritonitis"
Perforation	-if 5.2 = "Perforation"
Abdominal infection	-if 5.2 = "Abdominal abscess" or "Sepsis" or "Intestinal fistula" or "Phlegmon"
Intestinal obstruction	-if 5.2 = "Intestinal obstruction" or "Small bowel obstruction" or "Large bowel obstruction" or "Volvulus" or "Intussusception" or "Obstructing incisional hernia"
Haemorrhage	-if 5.2 = "Haemorrhage"
Ischaemia	-if 5.2 = "Ischaemia" or "Necrosis"
Other	-if 5.2 = "Colitis" or "Abdominal wound dehiscence" or "Abdominal compartment syndrome" or "Anastomotic leak" or "Other (Please give details)" or "Incarcerated hernia" or "Pneumoperitoneum" or "Pseudo-obstruction" or "Internal hernia" or "Acidosis" or "Iatrogenic injury" or "Foreign body"
Multiple indications	-if ≥2 of the above categories are 'Yes'