Postoperative Outcomes Within Enhanced Recovery After Surgery (POWER Study)

International observational cohort study of complications following elective gastrointestinal surgery within an enhanced recovery after surgery protocol

Study protocol version 1.0

October 2016

Short title *POWER study*

Sponsor: *Grupo Español de Rehabilitación Multimodal -GERM-. (ERAS Spain)*
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1. SIGNATURE PAGE

Principal Investigator Agreement

The clinical study as detailed within this research protocol **(Version 1.0, dated)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name: Javier Ripollés Melchor

Principal Investigator Site: Hospital Universitario Infanta Leonor, Madrid, Spain

Signature and Date:

2. SUMMARY/SYNOPSIS

Short title	POWER study
Methods	International, 30-day observational cohort study of postoperative complications following elective gastrointestinal surgery within an enhanced recovery after surgery protocol.
Research sites	Hospitals undertaking elective surgery worldwide and and performing ERAS protocol usually.
Objective	To provide detailed data describing post-operative complications and associated mortality; and length of stay. To provide detailed data describing adherence to ERAS protocol and its association to morbidity.
Number of patients	Not specified. All eligible patients undergoing surgery during the study month.
Inclusion Criteria	All adult patients (aged ≥18 years) undergoing gastrointestinal elective surgery within an ERAS protocol during the 30 day study period.

Statistical analysis	Univariate analysis will be used to test factors (patient, surgical, and ERAS related) associated with surgical complications, LOS and in-hospital death. Single and multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. A stepwise approach will be used to enter new terms. A single final analysis is planned at the end of the study. Summary statistics with post hoc Bonferroni corrections were used to assess possible dose–response dependence in percencentage of patients with postoperative complications and LOS
Proposed Start Date	A 30 day period between 2017

Proposed End Date	Data collection will end by August 2017
Study Duration	Four months

3. INTRODUCTION

Over 234 million major surgical procedures are performed globally each year1 and despite advances in surgical and anaesthetic care, morbidity after abdominal surgery is still high. Colorectal surgery is associated with a high risk of morbidity and mortality in comparison to other general surgery subspecialties. Overall mortality rates following colorectal surgery range from 1 to 16.4%,(15781793, 10813129, 26105552) with morbidity rates as high as 35%.(15781793, 10813129, 21806954). The concept of fast-track surgery, also called enhanced recovery after surgery (ERAS) or multimodal surgery involves using various perioperative strategies to facilitate better conditions for surgery and recovery in an effort to achieve faster discharge from hospital and more rapid resumption of normal activities after surgery through reducing postoperative stress and improving clinical practice by incorporating evidence-based medicine into patient management. ERAS protocols have repeatedly been shown to reduce length of stay 16363014; 21948187; 22882553) without influencing complication or readmission rates. 22882553, 17134506 Although individual components may vary, most of the ERAS programs include avoidance of fasting, preoperative optimization of health, preoperative carbohydrate loading, avoidance of bowel preparation, goal-directed hemodynamic therapy, multimodal analgesia with avoidance of opiates, avoidance/early removal of tubes (nasogastric tube, Foley catheter, and drains), support of gastrointestinal function, and early convalescence. 26346577 The development and widespread application of ERAS, in combination with laparoscopic surgery, represent a paradigm shift in perioperative care.1 Furthermore, the association between laparoscopic approach and ERAS perioperative management has recently proposed as the best option for patients undergoing segmental colectomy for colon cancer 17134506.

Our aim is to conduct an international 30-day cohort study of adults undergoing in-elective gastrointestinal surgery within an ERAS protocol to provide detailed data describing post- operative complications and associated mortality. Also, to determine how implementation of an ERAS program affects postoperative complications in patients undergoing elective gastrointestinal-surgery.

4. STUDY OBJECTIVES

Primary objective

To asses the incidence of 30-day postoperative complications following elective gastrointestinal surgery within an ERAS protocol.

Secondary objectives

1. To asses the 30-day in-hospital mortality associated with these complications
2. To describe the relationship between ERAS adherence and post- operative complications
3. To describe the effect of post-operative complications on duration of hospital stay

5. METHODS

International, observational, 30-day cohort study. Each national group will select a single 30-day period for patient recruitment between 2017.

Inclusion Criteria: All adult patients (aged ≥18 years) undergoing elective gastrointestinal surgery within an ERAS protocol in a participating hospital during the 30-day cohort period with a planned overnight stay.

Exclusion Criteria: Patients undergoing emergency surgery.

6. STUDY PROCEDURES

Consent procedures

The requirement for patient consent will vary according to regulations in the participating nations. We anticipate that patient consent will not be required most nations taking part in POWER on the basis that the dataset will only include variables documented as part of routine clinical care (see appendix) and that

identifiable patient data will not leave the hospital where each individual patient is treated. Unless written informed patient consent is provided, only anonymised or coded data will be provided to the POWER study group.

Country specific procedures for recruitment and patient consent

It is expected that worldwide, different countries have different regulatory requirements regarding patient consenting. Where required, the POWER study protocol will include country specific appendices to describe specific procedures regarding the use of identifiable patient data and the procedures involved and regulatory approvals required. Where individual patient consent is given for participation, it is recognised that this may provide the opportunity to link POWER data to national registry data on survival and other healthcare information. Plans for supplementary data collection in individual nations will also be detailed in a country specific appendix to this protocol.

Study data

Data will be collected on ***all eligible patients*** who undergo elective gastrointestinal surgery within ERAS during the study month. The proposed dataset is included in the appendix. Only routine clinical data will be included and where this is unavailable the domain will be left blank e.g. patients who do not require blood tests. It is possible that national groups may supplement their core data set with a very limited number of additional variables if these can be accommodated within the two page case record form (CRF) and they comply with regulations applied to this study.

Data collection

Data will be collected in individual hospitals on a paper CRF for each patient recruited. Paper CRFs will be stored within a locked office in each centre. This will include identifiable patient data in order to allow follow-up of clinical outcomes. Data will then be pseudo-anonymised by generating a unique numeric code and transcribed by local investigators onto an internet based electronic CRF. Each patient will only be identified on the electronic CRF by their numeric code. Thus the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. A patient list will be used in each centre to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points. Once the local co-ordinator confirms data entry is complete

for their hospital they will receive a spreadsheet of raw (un-cleaned) data, allowing further checks for data completeness and accuracy.

Study group organisation

POWER will be led by the study management group who will be responsible for study administration, communication between project partners, data collation and data management. National co-ordinators will lead the project in each nation and:

- Identify local co-ordinators in participating hospitals
- Assist with translation of study paperwork as required
- Ensure distribution of study paperwork and other materials
- Ensure necessary regulatory approvals are in place prior to the start date
- Ensure good communication with the participating sites in his/her nation

Local co-ordinators in individual institutions will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of eCRFs by supervising local data entry
- Communicate with the relevant national co-ordinator

End of Study Definition

The end of the study is defined as the end of the 30-day follow-up for the last patient included. Data analysis shall follow this.

7. STATISTICAL ANALYSIS

Sample size calculation

Our plan is to recruit as many centres as possible on an international basis and ask them to include all eligible patients in the study. A minimum of five centres from any country will be required for participation and only centres including 10 valid patients will be included in the data analysis. We do not have a specific sample size and statistical models will be adapted to the event rate provided by the sample recruited.

Statistical analysis

Hospitals including data describing less than 10 valid patients will be excluded in the data analysis. Data will be presented in individual nations. All national and institutional level data will be anonymised prior to publication. Categorical variables will be described as proportions and will be compared using chi-square or Fisher's exact test. Continuous variables will be described as mean and standard deviation, if normally distributed, or median and inter-quartile range, if not normally distributed. Comparisons of continuous variables will be performed using one-way ANOVA or Mann-Whitney test as appropriate. Univariate analysis will be performed to test factors associated with post-operative complications, LOS and in-hospital death. Single-level and hierarchical multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. Factors will be entered into the models based on their univariate relation to outcome ($p<0.05$), biological plausibility and low rate of missing data. A stepwise approach will be used to enter new terms. Results of logistic regression will be reported as adjusted odds ratios (OR) with 95% confidence intervals. The models will be assessed through the use of sensitivity analyses to explore possible interacting factors and examine any effect on the results. A single final analysis is planned at the end of the study.

Overall compliance was calculated as the average of all pre- and intraoperative

ERAS adapted elements, as specified in the ERAS society colon and rectal guidelines.(Table) For exploratory purposes, post-ERAS patients' guideline compliance was categorised into quintiles: compliance <45% (compliance 1), compliance 45-55 % (compliance 2), compliance 55-65 % (compliance 3), compliance 65-75 % (compliance 4) and compliance >75 % (compliance 5). Summary statistics with post hoc Bonferroni corrections were used to assess possible dose–response dependence in percencentage of patients with postoperative complications and LOS.

The data set will be analized using the percentage of patients with postoperative complications and LOS the main and secondary outcome variables. The influence of the following factors was assessed: sex, age, ASA status, BMI, preoperative hemoglobine, comorbidity, including hypertension , diabetes mellitus, coronary arterial disease , chronic obstructive pulmonary disease, and chronic renal disease; surgical approach (open, laparoscopic), duration of surgery, intraoperative fluid administration and first 24 hours fluid balance; and individual components of the

ERAS protocol. Univariate analysis will be initially undertaken to assess the relationship between each factor and the outcome variables. Comparisons will be made using the $\chi 2$ test for all categorical variables and the t test and Kruskall-Wallis test will be used to evaluate differences between continuous normally and non-normally distributed variables, respectively. Owing to its non-normal distribution, LOS was analyzed by log-normal transformation and independent t tests with back exponentiation. Multivariate analysis, using binary logistic regression for development of complications and linear regression of log transformed length of LOS, will be then performed for all variables in the univariate analysis with a significant or near-significant difference ($P < 0.1$). $P < 0.05$ was considered statistically significant.

Primary outcome measure

The percentage of patients who developed pre-defined mild-moderate-severe postoperative complications in the 30 days after surgery, including complications that occurred before hospital discharge and those that happened after discharge and required ambulatory or in-hospital care. Postoperative complications are defined according standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine (EPCO).

Secondary outcome measures

- In-hospital all-cause mortality (censored at 30 days following surgery)
- Adherence to ERAS items (within 30 days following surgery)
- Duration of hospital stay (duration of primary hospital stay after surgery)

8. ETHICS

The principal investigator must ensure that the study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. Research ethics approval may not be required in all participating nations. National and local investigators will be responsible for clarifying the need for ethics and other regulatory approvals and for ensuring these are in place prior to data collection. Centres will not be permitted to record data without providing confirmation that the necessary ethics or other regulatory approvals are in place. This study is, in effect, a large-scale clinical audit. We expect that in most, if not every participating country, there will be no requirement for individual patient consent as all data will be anonymised and are already recorded as part of routine clinical care. In countries that do require individual patient consent, it may be possible to collect data describing medium-term (e.g. one year) outcomes using healthcare registry data.

9. SAFETY CONSIDERATIONS

There are no safety considerations relating to the POWER study. There is no risk of harm to either patients or investigators.

10. DATA HANDLING AND RECORD KEEPING

All identifiable data collected, processed and stored for the purposes of the project will remain confidential at all times and comply with Good Clinical Practice for research (GCP) guidelines and the principles of the Data Protection Act 1998 (UK). Each centre will maintain a trial file including a protocol, local investigator delegation log, documentation of the relevant regulatory approvals and patient list. POWER data collection sheets will be stored securely in a locked cupboard and handled only by clinical staff familiar will handling personal data and with Good Clinical Practice for research. Data will be anonymised prior to transfer to the POWER study management group except where the patient has given written informed consent to allow transfer of identifiable data. Access to the data entry system will be protected by username and password, delivered during the registration process for individual local investigators. All electronic data transfer between participating centres and the co- ordinating centre will be encrypted using the SSL 3.0 protocol (HTTPS). Desktop

and laptop security will be maintained through user names and passwords. All local investigators will be asked to undergo training in accordance with the Research Governance Framework. The study master files will be stored in an approved repository for 20 years following the end of the study.

11. SAFETY REPORTING

The trial involves negligible risks to patients and investigators. Adverse events will not be monitored or reported.

12. MONITORING & AUDITING

POWER study master documents will be audited by the sponsor (Grupo Español de Rehabilitación Multimodal) to ensure study activities are conducted according to the protocol, the sponsor's standard operating procedures, Good Clinical Practice and the applicable regulatory requirements. In participating hospitals, local study documents may be selected for audit on a local basis. However, the POWER study team will not routinely monitor data collection in individual hospitals or conduct source data verification.

13. TRIAL COMMITTEES

Trial Management Group

The POWER trial will be managed by the Evidence Anesthesia Review Group (EAR) team based at Universidad Complutense de Madrid. The day-to-day conduct of the trial will be led by the trial management group, chaired by Javier Ripollés-Melchor.

Trial Steering Committee

The trial steering committee will be appointed with an independent chairperson (José María Calvo-Vecino), lay representation and independent members. There is no role for a Data Monitoring Committee.

14. FINANCE AND FUNDING

The POWER study is funded by an unrestricted research grant from Grupo Español de Rehabilitación Multimodal. The funder will play no role in study design, conduct, data collection, data analysis, reporting or interpretation of the results.

15. INDEMNITY

The POWERstudy is sponsored by Grupo Español de Rehabilitación Multimodal who has appropriate indemnity arrangements in place.

16. DISSEMINATION OF RESEARCH FINDINGS

The steering committee will appoint a writing committee to draft the scientific report(s) of this investigation, which will be disseminated in a timely manner. It is anticipated that a number of secondary analyses will be performed. POWER investigators will be given priority to lead such analyses and are encouraged to do so. Participation and authorship opportunities will be based on contribution to the primary study. The steering committee will consider the scientific validity and the possible effect on the anonymity of participating centres prior to granting any such requests. Where necessary, a prior written agreement will set out the terms of such collaborations. The steering committee must approve the final version of all manuscripts including POWER data prior to submission. In the event of disagreement within the steering committee, the chief investigator will make a ruling. Any analysis incorporating POWER data from two or more study sites will be considered a secondary analysis and subject to these rules. The eCRF will provide local co-ordinators with the raw (un-cleaned) data for their centre once they have confirmed this to be both complete and accurate.

Data management and ownership

The study sponsor, Grupo Español de Rehabilitación Multimodal, will act as custodian of the data. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to conduct secondary analyses. The primary consideration for such decisions will be the quality and validity of any proposed analysis. Only summary data will be presented publicly and all national, institutional and patient level data will be strictly anonymised. Individual patient data provided by participating

hospitals remain the property of the respective institution. Once each local co-ordinator has confirmed the data provided from their hospital are both complete and accurate, they will be provided with a spreadsheet of the raw (un-cleaned) data for their hospital. The complete POWER dataset, anonymised with respect to participating patients, hospitals and nations, will be made freely and publicly available two years following publication of the main scientific report. Prior to this, the steering committee is not under any obligation to release data to any collaborator or third party if they believe this is not in keeping with the wider aims of the POWER project.

17. REFERENCES

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APPENDIX 1. STATISTICAL ANALYSIS PLAN VERSION 1.0

1.0 Objectives

The primary objective of the study is to measure the incidence of 30-day postoperative complications following gastrointestinal surgery within ERAS protocol in the 180 days after surgery, including complications that occurred before hospital discharge and those that happened after discharge and required ambulatory or in-hospital care. The complications that will be analysed in this study are: infections, cardiovascular complications and other complications such as bleeding and acute kidney injury (please refer to EPCO definitions). The secondary objectives of this study include measuring the 30-day mortality and LOS associated with these complications and describing the incidence of complications for different adherence to the ERAS protocol. POWER will address the need to describe the frequency, severity and nature of complications following surgery and the associated short-term mortality.

2.0 Initial descriptive analysis

3.1 Participants

All participating hospitals have been asked to keep a log of the data that is collected. Data included in the study, missing data and completeness of follow up will be illustrated using a CONSORT flow diagram. The inclusion criteria are all adult patients (age≥18 years) undergoing elective gastrointestinal surgery within ERAS protocol in a participating hospital during the 30-day study period. Patients undergoing emergency surgery are excluded. Only hospitals returning valid data describing 10 or more patients will be included in the study. All eligible patients' data should be uploaded to the online e-CRF. A thorough data cleaning procedure will be implemented as follows:

- A robust e-CRF is designed to ensure data entry errors are minimised. The e-CRF provides a warning message and asks the user to confirm the value of any data entered which lie outside the pre-determined validity range.
- Checking for outliers. If there are extreme outliers, the data points will be excluded from the analysis. A secondary analysis will be conducted with all data included to gauge the difference in results.
- Duplicates will be checked for and removed using the software package SPSS Statistics 22.
- Handling of missing data is outlined in section 6.0.

3.2 Baseline characteristics

To give a broader understanding of the patients enrolled in the study, baseline characteristics of all the patients will be presented as outlined in Table 1. Numbers (%) or means (SD) and medians (IQR) will be given for each group as appropriate.

- Demographic: Age, sex, smoking status and American Society of Anesthesiologists (ASA) Physical Status grade
- Surgery related: Surgical procedure, laparoscopic surgery, cancer surgery, and duration of surgery.
- Co-morbidities: Presence of Hypertension, Diabetes Mellitus, Coronary Artery Disease, Heart failure, Cirrhosis, Metastasis cancer, Stroke or Transient Ischaemic Attack, COPD/Asthm..
- Pre-operative blood test results: haemoglobin, albumine, and creatinine.

3.0 Primary analysis

The primary outcome measure of this study is the percentage of patients with postoperative complications censored at 30 days after surgery. LOS, the number of deaths and the overall of complications within 30 days following the start of surgery will be reported. The primary effect estimate will be the odds ratio of 30-day, percentage of patients with postoperative complications, reported with 95% confidence intervals and p-value (Table 2). The significance level will be set at $p<0.05$.

A multivariable logistic regression analysis will be used to develop a generic model in which all biologically plausible predictor variables will be entered. With the expected large sample size, a large number of predictors can be included in the model without over fitting, thus predictors will be selected based on clinical suitability and assessment of correlated variables. The model will be adjusted for the following covariates: age, sex, smoking status,, surgical procedure category, ASA grade, presence of co-morbidities, anaesthetic technique, laparoscopic surgery, cancer surgery and baseline blood test results (namely haemoglobin, albumin and creatinine). For the purpose of this analysis will be grouped with upper gastrointestinal surgery and lower gastrointestinal surgery . All predictors will be entered into the model using forced simultaneous entry. To assess the reliability of our models, bootstrapping will be undertaken. To account for variations within countries, hospitals and patient groups and their influence on outcome, a three-level

hierarchical generalised linear mixed model will be used. Patients will be entered in the first level, hospitals in the second level and countries in the third level. This model will take into account the differences between countries and hospitals (e.g. among countries and hospitals) in relation to differences within those levels (e.g. among patients within hospitals). If this model fails to converge, a two level hierarchical model will be constructed with patients in the first level and countries in the second level. The results of the regression models will be reported with adjusted odds ratios, 95% confidence intervals and associated p-values. Unadjusted odds ratios will also be presented for comparison. To characterise the differences across hospitals, median odds ratio will also be reported for 30 days complications and mortality.

Residuals will be examined to ensure the assumptions for regression analyses are met. Goodness-of- fit for the models will be performed using the Hosmer-Lemeshow test. For multivariable regression analysis, multi-collinearity (correlations among predictor variables) is expected. Multi-collinearity will be assessed using the Variance Inflation Factor (VIF). This measures the extent to which the variance of the model coefficient will be inflated (due to correlation of the variable with the other predictor variables) if that variable is included in the model. A VIF>10 will be considered to be collinear and will be excluded from the analysis.

Overall compliance will be calculated as the average of all pre- and intraoperative ERAS adapted elements, as specified in the ERAS society colon and rectal guidelines.(Table) For exploratory purposes, post-ERAS patients' guideline compliance will be categorised into quintiles: compliance <45% (compliance 1), compliance 45-55 % (compliance 2), compliance 55-65 % (compliance 3), compliance 65-75 % (compliance 4) and compliance >75 % (compliance 5). Summary statistics with post hoc Bonferroni corrections were used to assess possible dose–response dependence in percencentage of patients with postoperative complications and LOS.

The data set will be analyzed using the percentage of patients with postoperative complications and LOS the main and secondary outcome variables. The influence of the following factors was assessed: sex, age, ASA status, BMI, preoperative hemoglobine, comorbidity, including hypertension , diabetes mellitus, coronary arterial disease , chronic obstructive pulmonary disease, and chronic renal disease; surgical approach (open, laparoscopic), duration of surgery, intraoperative fluid administration and first 24 hours fluid balance; and individual components of the ERAS protocol. Univariate analysis will be

initially undertaken to assess the relationship between each factor and the outcome variables. Comparisons will bemade using the χ2 test for all categorical variables and the t test and Kruskall-Wallis test will be used to evaluate differences between continuous normally and non-normally distributed variables, respectively. Owing to its non-normal distribution, LOS was analyzed by log-normal transformation and independent t tests with back exponentiation. Multivariate analysis, using binary logistic regression for development of complications and linear regression of log transformed length of LOS, will be then performed for all variables in the univariate analysis with a significant or near-significant difference ($P < 0.1$). $P < 0.05$ will be considered statistically significant. Differences in LOS between the pre-ERAS and ERAS groups will be also analyzed using Kaplan–Meier curves and log-rank tests as LOS was censored if the patient will decease.

4.0 Secondary analyses

4.1 Post-operative mortality

The number and percentage of deaths within 30 days of surgery will be reported for each surgical category (Upper or Lower). A logistic regression model with mortality as an outcome will be developed. The variable selection procedure will follow that of the primary analysis. The results will be reported as odds ratios with 95% confidence intervals and associated p-values.

4.2 All complications

The 30-day in-hospital complications that will be recorded in the e-CRF are: infectious complications, cardiovascular complications and other types of complications. Each complication will be graded as mild, moderate or severe. The overall incidence of each type and severity of complication and associated mortality rate will be reported (Table 4). Association between hospital mortality, complications and mortality after major complications will be analysed according to the method previously described by Ghaferi and colleagues. For this analysis, hospitals will be ranked anonymously according to their risk adjusted mortality rate and divided into five quintiles. For hospitals in each quintile, the incidence of overall and major complications and the rate of death among patients with major complications will be compared and reported.

4.5 Post-operative hospital stay

The median hospital length of stay (LOS) following the start of surgery, overall, by survival status and by complication status will be reported (Table 7). Post-operative LOS is the duration in days from the date of the end of surgery to the date of discharge from hospital.

5.0 Region Specific analysis

Data will be collected all countries. The number of participating sites and total number of patients for each region will be reported. Number and percentage of patients experiencing mortality and surgical complications within 30 days of surgery will be reported for each country (Table 9). This will help to provide an understanding of post-surgical care in different regions of the world. Post-operative complications and mortality will be documented for each country, but will not be published since the multivariable regression used in the primary analysis will adjust for country-level differences.

6.0 Handling of missing data

6.1 Data missing from database

A thorough approach will be undertaken by investigators to ensure completeness of data collection and data uploading. However, if data are still missing, then the following data handling technique will be used. If data are missing completely at random (MCAR), then case-wise deletion will be used to exclude the subjects from the analysis. Little's test will be used to investigate the patterns of the missing data.15 It tests whether data is MCAR or missing at random (MAR). If ≤5% of data is missing at random, then a complete case analysis will be conducted by excluding patients with missing data. If ≥5% of data is missing at random, then multiple imputation will be used. Multiple imputation substitutes a predicted value on the basis of other variables that are available for each subject.16 If data for any particular site are completely missing, then the site will be excluded from the analysis.

6.2 Sensitivity Analysis

A sensitivity approach will be taken if some data seem unrealistic. The primary analysis will

be repeated excluding these patients. If relevant outcome data are missing, such as complications, the primary analysis will be repeated once, assuming that all patients with missing outcome data had no complications. The analysis will then be repeated again with the opposite outcome. This will provide an understanding of how the findings may be affected if the data were complete.

APPENDIX 2. DEFINITION OF POSTOPERATIVE COMPLICATIONS

1.1 Acute Kidney Injury (AKI)

Definition. Kidney Disease Improving Global Outcomes (KDIGO) guidelines

1	Creat Clearance (Ç): 27 mmol L^{-1} (0.3 mg dl^{-1}) increase within 48 h.	
2	2.0–2.9 times baseline value within 7 days	Ç: 0.5 ml $kg^{-1}h^{-1}$
3	3.0 times baseline within 7 days	Ç: 0.3 ml kg^{-1} h^{-1}
	or	or
	Increase in serum creatinine to Ç: 354 mmol L^{-1} (Ç: 4.0 mg dl^{-1} with an acute rise of > 44 mmol L^{-1} (0.5 mg/dl^{-1})	Anuria for 12 h
	or	
	Initiation of renal replacement therapy	
	or	
	In patients < 18 years, decrease in eGFR to < 35 ml min^{-1} per 1.73 m^2	

1.2 Acute Respiratory Distress Syndrome (ARDS)

Definition. The Berlin definition of Respiratory Distress Syndrome.20

● Timing. Within one week of a known clinical insult or new or worsening respiratory symptoms and

● Chest imaging.a Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules and

● Origin of oedema. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present and

● Oxygenation.

○ Mild. PaO_2:FIO2 between 26.7 and 40.0 kPa (200-300 mmHg) with PEEP or CPAP = 5 cm H_2O.

○ Moderate. PaO_2: FIO_2 between 13.3 and 26.6 kPa (100-200 mmHg) with PEEP = 5 cm H_2O

○ Severe ↓PaO_2: FIO_2 < 13.3 kPa (100 mmHg) with PEEP = 5 cm H_2O

a) Chest radiograph or computed tomography scan.

b) If altitude is higher than 1000 m, a correction factor should be calculated (PaO_2: FiO_2 x [barometric pressure/101 kPa]).

c) This may be delivered non-invasively in the mild acute respiratory distress syndrome group.

Severity grading. Integrated in the above definition

1.3 Anastomotic breakdown

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

Severity*

1.4 Arrhythmia

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

Severity*

1.5 Cardiac arrest

Definition. The International Liaison Committee on Resuscitation defines cardiac arrest as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.23

Severity. Binary outcome.

1.6 Cardiogenic pulmonary oedema

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

Severity*

1.7 Deep vein thrombosis (DVT)

Definition. A new blood clot or thrombus within the venous system.

Severity*

1.8 Delirium

Definition. Delirium may be identified using the Intensive Care Delirium Screening Checklist. Patients are first evaluated for an altered level of consciousness. Those with a response to mild or moderate stimulation, an exaggerated response to stimulation or normal wakefulness are evaluated fully. Patients receive one point for each of the following criteria: inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance or symptom fluctuation. Delirium is diagnosed with a score

Severity grading. Integrated into definition.

1.9 Gastrointestinal bleed

Definition. Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz, in practice from the oesophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel or colon.
Severity*

1.10 Infection, source uncertain

Definition. The CDC defines infection, source uncertain as one where there is strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, meeting two or more of the following criteria: core temperature < 368C or >388C; white cell count >12 × 109 l—1 or < 4 × 109 l—1, respiratory rate >20 breaths per minute or PaCO2 < 4.7 kPa (35 mmHg); pulse rate >90 beats per minute
Severity*

1.11 Laboratory confirmed bloodstream infection

Definition. The CDC defines laboratory confirmed bloodstream infection as one which meets at least one of the following criteria which should not be related to infection at another site:

(1) Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site (2) Patient has at least one of the following signs or symptoms: fever >388C, chills or hypotension, and at least one of the following:

(a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions

(b) Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy

(c) Positive blood antigen test. Severity*

1.12 Myocardial infarction

Definition. Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria: 10 symptoms of ischaemia; new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus at angiography or autopsy.

Severity*

1.13 Myocardial injury after non-cardiac surgery (MINS)

Definition. Peak troponin T (TnT) Ç0.03 ng ml—1 judged due to myocardial ischaemia (i.e. no evidence of a non- ischaemic aetiology causing the TnT elevation). This criterion excludes troponin abnormalities related to other causes. Severity. Binary outcome.

1.14 Pneumonia

Definition. The CDC defines pneumonia as follows:

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

(1) new or progressive and persistent infiltrates
(2) consolidation
(3) cavitation;

at least one of the following

(1) fever (>388C) with no other recognised cause
(2) leucopaenia (white cell count < 4×10^9 L^{-1}) or leucocytosis (white cell count > 12×10^9 L^{-1})
(3) for adults >70 years old, altered mental status with no other recognised cause;

and at least two of the following

(1) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
(2) new onset or worsening cough, or dyspnoea, or tachypnoea
(3) ra les or bronchial breath sounds
(4) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand).

Severity*

1.15 Paralytic ileus

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

Severity*

1.16 Postoperative haemorrhage

Definition. The ACS-NSQIP defines postoperative haemorrhage as blood loss within 72 h after the start of surgery which would normally result in transfusion of blood
Severity* (mild excluded)

1.17 Pulmonary embolism (PE)

Definition. A new blood clot or thrombus within the pulmonary arterial system. Guidance. We did not identify a suitable definition for postoperative PE in the literature. Treatment is often determined by clinical risk of PE rather than a definitive diagnosis. Systematic screening is required in trials where PE is an important outcome measure. Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery.
Severity*

1.18 Stroke

Definition. The ACS-NSQIP defines stroke as an embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).
Severity*

1.19 Surgical site infection (superficial)

Definition. The CDC defines a superficial incisional surgical site infection as one which meets the following criteria.
(1) Infection occurs within 30 days after surgery and

(2) Involves only skin and subcutaneous tissue of the incision and (3) The patient has at least one of the following:
(a) purulent drainage from the superficial incision
(b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision

(c) at least one of the following symptoms or signs of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.

(d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.
Severity*

1.20 Surgical site infection (deep)

Definition. The CDC defines a deep incisional surgical site infection as one which meets the following criteria.
(1) Infection occurs within 30 days after surgery if no implant is left in place or 1 year if implant is in place.
(2) Involves deep soft tissues (e.g. fascial and muscle layers) of the incision. (3) The patient has at least one of the following:
(a) purulent drainage from the deep incision but not from the organ/space component of the surgical site
(b) a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following symptoms or signs: fever (>388C), or localised pain or tenderness. A culture-negative finding does not meet this criterion.
(c) an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathological or radiological examination
(d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.
Severity*

1.21 Surgical site infection (organ/space)

Definition. The CDC defines an organ/space surgical site infection as one which involves any part of the body excluding the fascia or muscle layers and meets the following criteria:

(1) Infection occurs within 30 days after surgery.

(2) The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia or muscle layers opened or manipulated during the operative procedure.

(3) The patient has at least one of the following:

(a) purulent drainage from a drain that is placed through a stab wound into the organ/space

(b) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space

(c) an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathological or radiological examination

(d) diagnosis of an organ/space surgical site infection by a surgeon or attending physician

Severity*

1.22 Urinary tract infection

Definition. A simplified version of the CDC recommendations defines a urinary tract infection as follows: a positive urine culture of Ç105 colony forming units ml^{-1} with no more than two species of micro-organisms, and with at least one of the following symptoms or signs: fever (>388C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause

Severity*

Severity*

Severity grading

Mild: Results in only temporary harm and would not usually require specific clinical treatment.

Moderate: More serious complication but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. Severe: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.

APPENDIX 3. : Dummy tables and figures

Figure 1: Flow diagram

	All patients (n%)	Complications (n%)	Died in hospital (n%)
Age, mean (SD)			
Male			
Female			
Smoker			
ASA Score			
I			
II			
III			
IV			
Surgical Procedure category			
Upper gastrointestinal			
Plastics/Cutaneous			
Chronic Comorbid disorder			
Coronary Artery Disease			
Congestive Heart Failure			
Diabetes Mellitus			
Cirrhosis			
Metastatic Cancer			
Stroke or Transient Ischaemic Attack			
COPD / Asthma			
Hypertension			
Blood test results			
Haemoglobin (mean)			
Albumin (mean)			
Creatinine (mean)			

Table 1:
Baseline characteristics

Table 2: ERAS compliance

Protocol adherente n, %	All patients (n%)	Complications Ns (%)	Died in hospital (n%)
Preoperative information, education and counselling			
Preoperative optimization			
Preoperative bowel preparation			
Preoperative fasting and carbohydrate treatment			
Preanestesic medication			
Prophylaxis against thromboembolism			
Antimicrobial prophylaxis and skin preparation			
Standard anaesthetic protocol			
Postoperative nausea and vomiting prophylaxis			
Laparoscopy and modifications of surgical access			
Nasogastric intubation			
Preventing intraoperative hypothermia			
Perioperative fluid management			
Drainage of peritoneal cavity after colonic anastomosis			
Urinary drainage			
Prevention of postoperative ileus			
Postoperative analgesia			
Perioperative nutritional care			
Postoperative glucose control			
Early mobilisation			

Table 3: Postoperative complications

	Any complication (n%)	Mild (n%)	Moderate (n%)	Severe (n%)	30-day mortality (n%)
Infectious complications					
Superficial					
Deep surgical site					
Body cavity					
Pneumonia					
Urinary tract					
Bloodstream					
Cardiovascular complications					
Myocardial					
Arrhythmia					
Pulmonary					
Pulmonary					
Stroke					
Cardiac arrest		N/A	N/A		
Other complications					
Gastro-intestinal					
Acute kidney					
Post-operative		N/A			
ARDS					
Anastomotic leak					
All others					

Table 4. Mortality

	30-day in-hospital mortality		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Upper gastro-intestinal			
Lower gastro-intestinal			

Table 5. LOS

	30-day in-hospital mortality		
	Unadjusted OR (95% CI)	Adjusted OR (95%CI)	p-value
Upper gastro-intestinal			
Lower gastro-intestinal			

Table 6. Univariate analysis

	Postoperative complications			LOS		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Patient factors						
Male						
Age						
ASA						
BMI						
Hb						
Hypertension						
DM						
Coronary artery disease						
COPD						
Chronic kidney diseasse						
Surgical factors						
Laparoscopy						
Duration						
Intraoperative fluids						
24 hours fluids						
Perioperative 24 hours fluid balance						
ERAS factors						
Preoperative information,						
Education and counselling						
Preoperative fasting and						
carbohydrate treatment						
Preanestesic medication						
Prophylaxis against thromboembolism						

Antimicrobial prophylaxis and skin preparation						
Standard anaesthetic Protocol						
Postoperative nausea and vomiting prophylaxis						
Laparoscopy and modifications of surgical						

Preventing intraoperative hypothermia						
Perioperative fluid management						
Drainage of peritoneal cavity after colonic						
Urinary drainage						
Prevention of postoperative ileus						
Postoperative analgesia						
Perioperative nutritional care						
Postoperative glucose control						
Early mobilisation						

Table 7. Multivariate analysis

	Postoperative complications			LOS		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Male						
Age						
ASA						
BMI						
Hb						
Hypertension						
DM						
Coronary artery disease						
COPD						
Chronic kidney diseasse						
Surgical factors						
Laparoscopy						
Duration						
Intraoperative fluids						
24 hours fluids						
Perioperative 24 hours fluid balance						
ERAS factors						
Preoperative information,						
Education and counselling						
Preoperative fasting and						
carbohydrate treatment						
Preanestesic medication						
Prophylaxis against thromboembolism						
Antimicrobial prophylaxis and skin preparation						

Standard anaesthetic Protocol						
Postoperative nausea and vomiting prophylaxis						
Laparoscopy and modifications of surgical						
Nasogastric intubation						

Preventing intraoperative hypothermia						
Perioperative fluid management						
Drainage of peritoneal cavity after colonic						
Urinary drainage						
Prevention of postoperative ileus						
Postoperative analgesia						
Perioperative nutritional care						
Postoperative glucose control						
Early mobilisation						

Table 8. Region specific analysis

	Number of participati ng sites (n)	Number of patients (n%)	30-day complicatio ns (n%)	30-day in-hospital mortality (n%)
Spain				
France				
UK				
Italy				
x				
x				
x				
x				
x				
x				
x				
x				
x				

- **Example Case Record Form**

Age **years** **Gender # M # F** **Current smoker # Y # N**

BMI _____ **ASA I II III IV V**

Black ethnicity (eGFR) Y N

Chronic Co-Morbid Disease (tick all that apply):

 # Coronary Artery Disease **# Congestive Heart Failure**
 # Diabetes Mellitus **# Cirrhosis**
 # Metastatic cancer **# Stroke or Transient Ischaemic Attack**
 # COPD / Asthma **# Hypertension**

Most recent blood results (no more than 28 days before surgery):

Haemoglobin: **g/L** **Albumin:** **mmol/L**

Creatinine: **µmol/L ***

Anaesthesia induction time & date: H H m m D D M M 2 0 1 6

Anaesthetic technique (tick all that apply):

 # General # Spinal # Epidural # Sedation / Local # Other regional

Surgical procedure category (*single* best answer):

 # Upper gastro-intestinal **# Lower gastro-intestinal**

Laparoscopic surgery: **# Y** **# N**

Cancer surgery: **# Y** **# N**

Table 9. Adherence

Protocol adherence	Y/N
Preoperative bowel preparation	
Preoperative fasting and carbohydrate treatment	
Preanestesic medication	
Prophylaxis against thromboembolism	
Antimicrobial prophylaxis and skin preparation	
Standard anaesthetic protocol	
Postoperative nausea and vomiting prophylaxis	
Laparoscopy and modifications of surgical access	
Nasogastric intubation	
Preventing intraoperative hypothermia	
Perioperative fluid management	
Drainage of peritoneal cavity after colonic anastomosis	
Urinary drainage	
Postoperative analgesia	
Perioperative nutritional care	
Postoperative glucose control	
Early mobilisation	

Table 10. Follow Up

Post-operative Follow Up				
Infection				
Wound infection	Mild #	Moderate #	Severe #	None #
Body cavity	Mild #	Moderate #	Severe #	None #
Pneumonia	Mild #	Moderate #	Severe #	None #
Urinary tract	Mild #	Moderate #	Severe #	None #
Bloodstream	Mild #	Moderate #	Severe #	None #
Cardiovascular				
Myocardial infarction	Mild #	Moderate #	Severe #	None #
Arrhythmia	Mild #	Moderate #	Severe #	None #
Pulmonary oedema	Mild #	Moderate #	Severe #	None #
Pulmonary embolism	Mild #	Moderate #	Severe #	None #
Cardiac arrest	Mild #	Moderate #	Severe #	None #
Stroke	Mild #	Moderate #	Severe #	None #
Other				
Gastro-intestinal bleed	Mild #	Moderate #	Severe #	None #
Other post-operative bleed	Mild #	Moderate #	Severe #	None #
Acute kidney injury	Mild #	Moderate #	Severe #	None #
Delirium	Mild #	Moderate #	Severe #	None #
ARDS	Mild #	Moderate #	Severe #	None #
Anastomotic leak	Mild #	Moderate #	Severe #	None #
Medical error	Mild #	Moderate #	Severe #	None #
Other	Mild #	Moderate #	Severe #	None #

Duration of hospital stay after surgery (days):

Survival at 30 days after surgery: **# Alive** **# Dead**