International Surgical Outcomes Study (ISOS)

International observational cohort study of complications following elective surgery

Statistical Analysis Plan Version 1.0

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Short title	*ISOS study*
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1.0 Background

Over 230 million patients undergo surgery worldwide each year with reported hospital mortality between 1 and 4%.[1-4] Complications following major surgery are a leading cause of morbidity and mortality.[5-10] In the overall surgical population, the incidence of post-operative complications and death is low. However, studies suggest the existence of a high-risk sub-group of surgical patients which accounts for 80% of post-operative deaths but less than 15% of in-patient procedures.[8, 9] Patients who develop complications but survive to leave hospital often suffer reductions in functional independence and long-term survival.[5-7] In the Whitehall II study, British civil servants who took sickness absence from work were followed up for long-term survival. Sickness absence to undergo surgery was second only to cardiovascular disease in terms of associated long-term mortality.[5] Data from the National Surgical Quality Improvement Programme in the USA suggest that survival amongst patients who develop post-operative complications varies between hospitals, suggesting both the potential and the need to improve clinical outcomes in this population.[11] With the high volumes of surgery performed, even a low rate of avoidable harm will be associated with a large number of preventable deaths. There is increasing recognition of the massive potential impact of even small improvements in peri-operative care.[12]

A recent study provided the first report of post-operative outcomes at a European level (EuSOS).[3] The findings of this study suggest that post-operative mortality may be higher than previously thought and that mortality may vary between nations, again suggesting preventable deaths may occur. However, the EuSOS dataset did not include complications following surgery. The study group made a pragmatic decision to focus on the most readily collectable data with detailed follow-up of those patients admitted to the critical care unit. EuSOS was also confined to nations in geographical Europe. As a result, our understanding of peri-operative outcomes at an international level is incomplete and the need remains for data describing the frequency, severity and nature of complications following surgery and the associated short-term mortality. Our aim is to conduct an international seven-day cohort study of adults undergoing in-patient elective surgery to provide detailed data describing postoperative complications and associated mortality.

ISOS is an international seven-day prospective cohort study designed to assess post-operative complications and mortality in adult patients following elective surgery. The anticipated sample size

is 50,000 patients from 32 different countries around the world. Each national group will select a single seven-day period for patient recruitment between April and June 2014. The end of the study will be defined as the end of the 30-day period follow up period for the final participant in the study. This document is the proposed statistical analysis plan for the ISOS study. The purpose of this statistical analysis plan is to set out the proposed analysis in advance of inspecting the data so that data derived decisions are avoided.

2.0 Objectives

The primary objective of the study is to measure the incidence of 30-day complications following in-patient surgery. 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 eCRF v2.3). The secondary objectives of this study include measuring the 30-day mortality associated with these complications and describing the incidence of complications for different surgical specialties. ISOS will address the need to describe the frequency, severity and nature of complications following surgery and the associated short-term mortality while extending geographically to include countries outside of Europe.

3.0 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 surgery in a participating hospital during the seven-day study period with a planned overnight stay. Patients undergoing emergency surgery, planned day-case surgery or radiological procedure are excluded. Only hospitals returning valid data describing 20 or more patients will be included in the study. Following a discussion within the ISOS steering committee, it was decided that the inclusion of countries with fewer than ten participating hospitals should be decided on a case-by-case basis.

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 (hard and soft ranges), e.g. if haemoglobin is less than 30 g/L or age greater than 100 years.
- 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, severity of surgery and duration of surgery.
- Co-morbidities: Presence of Diabetes Mellitus, Coronary Artery Disease, Heart failure, Cirrhosis, Metastasis cancer, Stroke or Transient Ischaemic Attack, COPD/Asthma and other co-morbidities.
- Pre-operative blood test results: haemoglobin, leucocytes, sodium and creatinine.

3.0 Primary analysis

The primary outcome measure of this study is in-hospital complications censored at 30 days after surgery. The number of deaths and percentage 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 post-operative 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, severity of surgery, surgical procedure category, ASA grade, presence of co-morbidities, anaesthetic technique, laparoscopic surgery, cancer surgery and baseline blood test results (namely haemoglobin, leucocytes, sodium and creatinine). For the purpose of this analysis, thoracic (gut) will be grouped with upper gastrointestinal surgery, leaving thoracic (lung) only in the thoracic group. All predictors will be entered into the model using forced simultaneous entry. To assess the reliability of our models, bootstrapping will be undertaken.[13] 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.[14]

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.

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 (Table 3). 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. [11]

4.3 Infectious complications

The post-operative infectious complications that will be recorded in the e-CRF are surgical site infection, body cavity, pneumonia, urinary tract infection and bloodstream infection. The number and percentages of patients developing infectious complications within 30 days of surgery for different surgical categories will be reported (Table 5). Differences in 30-day infectious complications for different surgical procedure categories will be compared and adjusted using a logistic regression model. A dummy variable for each surgical category will be entered into the logistic regression model. The results will be reported as adjusted odds ratios with 95% confidence intervals and associated p-values. The most common type of infection for each surgical category will also be reported (Table 5).

4.4 Cardiovascular complications

The number and percentage of patients developing a cardiovascular complication within 30 days following the start of surgery will be reported for all surgical categories (Table 6). The cardiovascular complications are graded as mild, moderate and severe. The number and percentages of patients developing cardiovascular complications within 30 days following the start of surgery will be reported for the different surgical categories. The likelihood of developing cardiovascular complications within 30 days of surgery for the different surgical procedure categories will be compared and adjusted using a logistic regression model. A dummy variable for each category of surgery will be entered into the logistic regression model. The results will be reported as adjusted odds ratios with 95% confidence intervals. The most frequent cardiovascular complication will also be reported with the number and percentage of patients suffering from that particular complication.

4.5 Post-operative hospital stay & admission to critical care

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. The number and percentage of complications, mortality and median LOS for patients in critical care will also be presented, but will not be subjected to any statistical tests (Table 7).

4.6 Analysis without ASA classification

The ASA physical status classification system assesses the fitness of patients before surgery. In 1963, the American Society of Anaesthesiologists adopted the five category physical status classification system; a sixth category was added later. ASA grades V and VI are excluded as the study is confided to elective surgery. The categories are:

I - A normal healthy patient

II - A patient with mild systemic disease

III - A patient with severe systemic disease

IV - A patient with severe systemic disease that is a constant threat to life

The primary analysis will be repeated without adjusting for ASA grading. This will be done to understand relative contribution of individual diseases and how it relates to co-morbidities.

4.7 Treatment for post-operative complications (Clavien-Dindo grading)

Data required to classify complications according to the Clavien-Dindo grading system will also be available. The Clavien-Dindo grading system classifies surgical complications in patients according to the post-surgical treatment received. The number and percentage of patients in each Clavien-Dindo grade will be reported (Table 8). A sensitivity analysis will be conducted by repeating the primary analysis using Clavien-Dindo grading to classify complications. This will provide an understanding of how the findings are affected by the use of a different system of evaluating complications.

5.0 Region Specific analysis

Data will be collected from the following geographical regions: Australasia, North America, Central & South America, Western Europe, Eastern Europe, Northern Europe, Southern Europe, Indian sub-continent, Middle East, China & South-East Asia, North Africa, Sub-Saharan Africa and Central Asia. 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 region (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.

7.0 Health economics measures

To evaluate whether post-operative complications and risk-adjusted mortality can be influenced by health economics measures such as income, healthcare system and healthcare inequalities at a country level, we will assess these outcomes according to recognised economic measures. To assess how income is associated with post-operative complications and mortality, countries will be anonymously ranked according to gross domestic product (GDP) and divided into quartiles. The post-operative complication rates and mortality will be compared and reported for each quartile.

Similarly, to understand healthcare systems factors which may affect patient outcomes, countries will be ranked according to doctors per capita and divided into quartiles. Then the post-operative complication and mortality rate will be compared across quartile.

To assess how health inequality is associated with post-operative complications and mortality, countries will be anonymously ranked according to the Gini coefficient. The Gini coefficient is a number between zero (or 0%) and one (or 100%), where zero corresponds with perfect equality (where everyone has the same income) and one (or 100%) corresponds with perfect inequality (where one person has all the income and everyone else has zero income). Countries will be ranked according to their Gini coefficient and divided into quartiles. Each quartile's post-operative complication rate and mortality rate will be compared. World Health Bank data will be used to obtain the measures for each country. The results of each health economics measure will be summarised and presented in Table 10.

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Appendix 1: Dummy tables and figures

Figure 1: Flow diagram

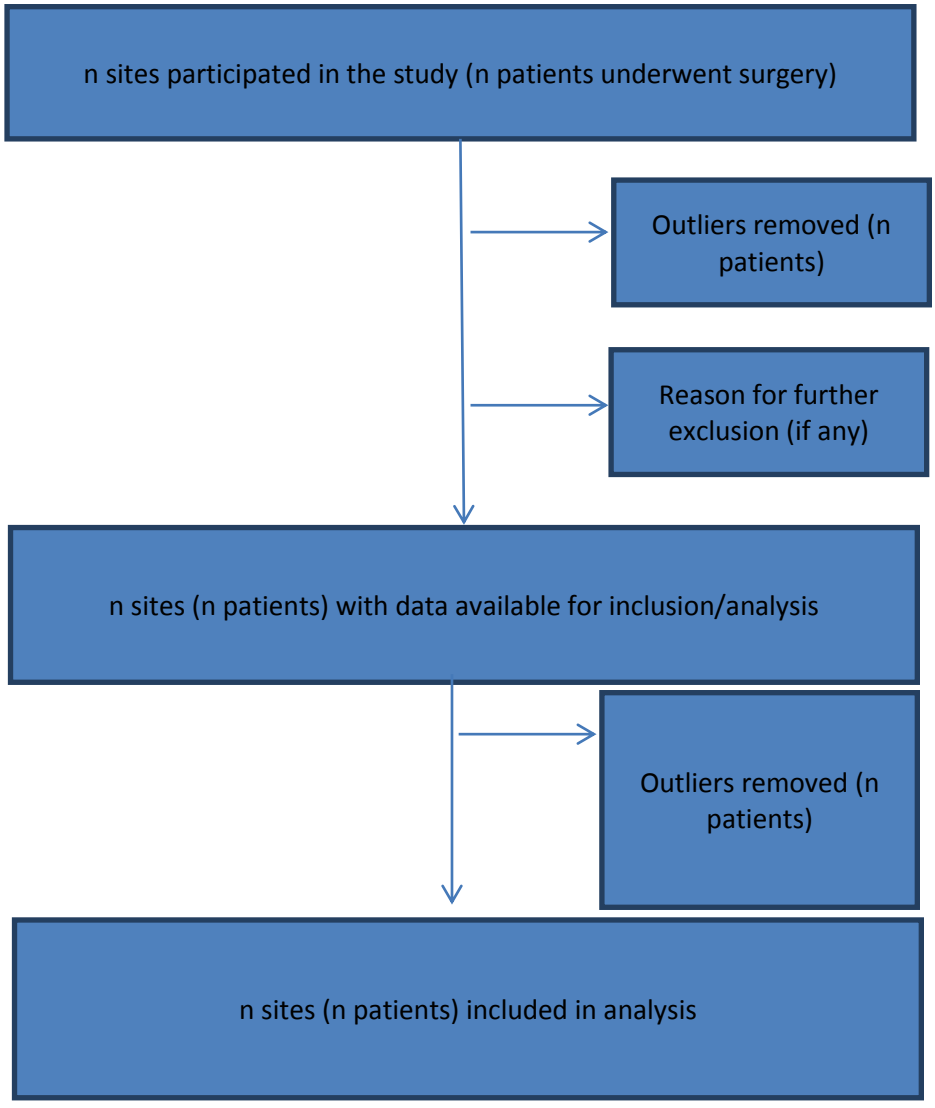

Table 1: Baseline characteristics

	All patients (n%)	Complications (n%)	Died in hospital (n%)
Age, mean (SD)	Xxx	xxx	xxx
Male			
Female			
Smoker			
Ethnicity			
Black			
ASA Score			
I			
II			
III			
IV			
Severity of surgery			
Minor			
Intermediate			
Major			
Surgical Procedure category			
Orthopaedic			
Breast			
Thoracic			
Obstetrics & Gynaecology			
Upper gastro-intestinal			
Lower gastro-intestinal			
Hepato-biliary			
Vascular			
Urology & Kidney			
Head & Neck			
Cardiac			

Plastics/Cutaneous			
Chronic Comorbid disorder			
Coronary Artery Disease			
Congestive Heart Failure			
Diabetes Mellitus			
Cirrhosis			
Metastatic Cancer			
Stroke or Transient Ischaemic Attack			
COPD/Asthma			
Other			
Blood test results			
Haemoglobin (mean)			
Leucocytes (mean)			
Sodium (mean)			
Creatinine (mean)			
Other measures			
Surgical Checklist used			
Laparoscopic Surgery			
Cancer surgery			

Table 2: Primary outcome: In-hospital complications in various surgical specialties

	Post-operative complications		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Orthopaedic			
Breast			
Thoracic			
Obstetrics & Gynaecology			
Upper gastro-intestinal			
Lower gastro-intestinal			
Hepato-biliary			
Vascular			
Urology & Kidney			
Head & Neck			
Cardiac			
Plastics/Cutaneous			
Thoracic (lung & cancer)			

Table 3: Secondary Analysis: 30-day in-hospital mortality for each surgical speciality

	30-day in-hospital mortality		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Orthopaedic			
Breast			
Thoracic			
Obstetrics & Gynaecology			
Upper gastro-intestinal			
Lower gastro-intestinal			
Hepato-biliary			
Vascular			
Urology & Kidney			
Head & Neck			
Cardiac			
Plastics/Cutaneous			
Thoracic(lung & cancer)			

Table 4: Outcomes after surgery

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

Table 5: 30-day in-hospital infectious complications

	Adjusted OR for infectious complication (95% CI)	p-value	Most common infection (n%)
Orthopaedic			
Breast			
Thoracic			
Obstetrics & Gynaecology			
Upper gastro-intestinal			
Lower gastro-intestinal			
Hepato-biliary			
Vascular			
Urology and Kidney			
Head & Neck			
Cardiac			
Plastics/Cutaneous			
Thoracic (lung & cancer)			

Table 6: 30-day in-hospital cardiovascular complications

	Adjusted OR for cardiovascular complication (95% CI)	p-value	Most frequent complication (n%)
Orthopaedic			
Breast			
Thoracic			
Obstetrics & Gynaecology			
Upper gastro-intestinal			
Lower gastro-intestinal			
Hepato-biliary			
Vascular			
Urology and Kidney			
Head & Neck			
Cardiac			
Plastics/Cutaneous			
Thoracic (lung & cancer)			

Table 7: Post-operative hospital measures

	Number of days (median)	Number of patients (n%)
Hospital stay for all patients		
Hospital stay for patients with a complication		
Hospital stay for patients who died		
Length of critical care stay		
Hours in Post-Anaesthetic Care Unit		
Admission to critical care immediately after surgery*	N/A	
In-hospital mortality for critical care patients*	N/A	
In-hospital complications for critical care patients*	N/A	

*Only applies to planned critical care admission immediately after surgery and not where patients are admitted to critical care in order to treat post-operative complications

Table 8: Clavien-Dindo classification of treatment

	Number of patients (n%)	Adjusted odds ratio of post-operative complication (95% CI)	Adjusted odds ratio of mortality (95% CI)	p-value
No complications				
Grade I				
Grade II				
Grade III				
Grade IV				
Grade V				

Table 9: Region specific analysis

	Number of participating sites (n)	Number of patients (n%)	30-day complications (n%)	30-day in-hospital mortality (n%)
Eastern Europe				
Western Europe				
Northern Europe				
Southern Europe				
North America				
Central & South America				
China & South-East Asia				
Central Asia				
Indian sub-continent				
Sub-Saharan Africa				
North Africa				
Australasia				
Middle East				

Table 10: Health economics analysis

		Post-operative complication rate (n%)	Mortality rate (n%)
Income bracket	**GDP* range**		
Top 25%			
25% - 50%			
50% - 75%			
Bottom 25%			
Number of doctors per capita	**Number of doctors**		
1st quartile			
2nd quartile			
3rd quartile			
4th quartile			
Gini coefficient	**Gini coefficient**		
1st quartile			
2nd quartile			
3rd quartile			
4th quartile			

*GDP – Gross Domestic Product