

# International Surgical Outcomes Study (ISOS) sub-study: post-operative infection

## Statistical analysis plan

### Working title

Prospective observational cohort study of post-operative infection and mortality following elective surgery within ISOS

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## Background

There are more than 310 million surgical procedures worldwide each year.<sup>1</sup> In the UK, one in ten adults has a surgical procedure each year, and the annual number of procedures is increasing steadily.<sup>2</sup> Estimates of post-operative morbidity and mortality vary, but approximately seven million patients worldwide experience a post-operative complication each year.<sup>3-5</sup> Post-operative infections increase morbidity and mortality, and prolong intensive care and hospital stays.<sup>6</sup>

Post-operative infections are an important cause of post-operative death, although estimates vary widely. For example, organ space infection has reported mortality rates between 4 and 9%, and mortality ranges from 28 to 46% in those patients who progress to septic shock.<sup>7 8</sup> Many post-operative infections do not progress to severe sepsis or septic shock and the mode of death for such patients is unclear. Previously reported rates of mortality for different types of infection vary widely depending on the population. The literature remains unclear about the overall rates of post-operative infection and subsequent outcomes. The relationships between different types of infection, surgical procedures, and other adverse outcomes are also unclear.

There are few large epidemiological studies which explore the risk factors and outcomes of post-operative infection. Increasing knowledge and ability to provide accurate and generalisable estimates of the key risk factors for infection and subsequent patient outcomes will aid prevention of serious post-operative infections, particularly on a global level

The International Surgical Outcomes Study aimed to provide a detailed description of post-operative complications across a large international cohort.<sup>9</sup> The aim of this secondary analysis is to describe the prevalence of post-operative infection in an international sample of surgical patients. We will also investigate risk factors for the development of infection and the association between infection and morbidity and mortality following elective surgery.

## **Aim**

To describe the incidence and types of post-operative infection which occur following elective surgery; baseline risk factors for its development; and its association with adverse clinical outcomes within 30 days (specific endpoints defined below).

## **Objectives**

1. To describe the incidence, type, and severity of post-operative infection
2. To identify baseline risk factors for the development of post-operative infection:
  - patient characteristics
  - anaesthetic and surgical factors
3. To determine 30-day mortality for patients who do and do not develop different types of post-operative infection
4. To determine if post-operative infection influences process measures
  - critical care length of stay
  - hospital length of stay

## **Data collection**

### *Study cohort*

The International Surgical Outcome Study (ISOS) is an international multi-centre cohort study of perioperative morbidity and mortality in patients undergoing elective surgery (ISRCTN51817007).<sup>9</sup> Data collection occurred during a seven-day period between April and August 2014 in 474 hospitals in 27 countries. All patients admitted to participating centres for elective surgery with a planned overnight stay were eligible. Patients undergoing day-case surgery or radiological procedures were excluded because they followed a dedicated pathway of care. The total sample size collected is 44,863. Patients were followed up for a maximum of 30 days after surgery.

### *Sample*

The dataset for this secondary analysis includes only patients from the ISOS cohort with mortality outcome data resulting in a sample size of 44,814.

### *Key variables*

The paper case report form (CRF) is shown in appendix 1. Independent variables which will be included in analyses for patient characteristics and anaesthetic and surgical factors are listed in table (i). The outcome variable infection is a composite measure of six different types of infection where more than

one type can occur in the same patient: superficial surgical site, deep surgical site, body cavity, pneumonia, urinary tract, and bloodstream. Each type is graded by severity (mild/moderate/severe/none). Additional outcomes measures will include mortality, critical care length of stay and hospital length of stay.

Three variables are listed for treatment for post-operative complications:

Drug therapy, blood transfusion or parenteral nutrition (Y/N)

Surgical or radiological procedure (Y/N)

Critical care admission (Y/N)

We will only look at this variable in the subset of patients who did not have any other complications not related to infection: cardiovascular or other complications. This is to ensure that any variable selected for treatment for post-operative complications is due to treatment for an infective complication.

Table (i). List of key independent variables.

Variable	Type of data	Note
<b>Patient characteristics</b>		
Age in years	Continuous	
Sex (M/F)	Binary	
Current smoker (Y/N)	Binary	
ASA (I-IV)	Categorical	
Coronary artery disease (Y/N)	Binary	Chronic disease diagnosis
Diabetes mellitus (Y/N)	Binary	
Metastatic cancer (Y/N)	Binary	
COPD/asthma (Y/N)	Binary	
Heart failure (Y/N)	Binary	
Cirrhosis (Y/N)	Binary	
Stroke (Y/N)	Binary	
Other (Y/N)	Binary	
Haemoglobin g/L	Continuous	Most recent blood result
Sodium mmol/L	Continuous	
Leukocytes $\times 10^9/L$	Continuous	
Creatinine $\mu\text{mol/L}$	Continuous	
<b>Anaesthetic and surgical factors</b>		
General anaesthetic	Binary	Anaesthetic technique
Spinal	Binary	
Epidural	Binary	
Sedation/local	Binary	
Surgical procedure (Orthopaedic/Breast/Obstetrics and gynaecology/Urology and kidney/Upper gastro-intestinal/Lower gastro-intestinal/Hepato-biliary/Vascular/Head and neck/Plastics and cutaneous/Cardiac/Thoracic/Other)	Categorical	
Severity of surgery (Minor/Intermediate/Major)	Categorical	
Laparoscopic surgery (Y/N)	Binary	
Cancer surgery (Y/N)	Binary	
Surgical checklist used (Y/N)	Binary	
Critical care immediately after surgery (Y/N)	Binary	

## Statistical analysis

Baseline characteristics for patients who experienced no infection compared to infection will be summarised but not subjected to statistical testing. Numbers (%), means (SD) and medians (IQR) will be provided separately for each group. Incidence of infection will be presented by type and severity.

The primary outcome will be the development of post-operative infection within 30 days following surgery. The primary outcome will be defined as being recorded if data are available for each of the following components:

- Superficial surgical site
- Deep surgical site
- Body cavity
- Pneumonia
- Urinary tract
- Bloodstream

The primary outcome is defined as missing if data are missing for the above six components. Cases missing outcome data for post-operative infection will be excluded from the analysis (Figure 1).

The primary outcome will be analysed using a mixed effects logistic regression model, with a random intercept for country and site. The model will be adjusted for the following pre-specified baseline covariates: age, gender, coronary artery disease, heart failure, diabetes mellitus, cirrhosis, metastatic cancer, stroke, COPD/asthma, other co-morbid diseases, ASA score (I & II vs. III & IV), surgical procedure, severity of surgery. Age will be included as a continuous variable, assuming a linear association with the outcome. Categorical variables with two or more categories will be included using indicator variables. Results will be presented as odds ratios with a 95% confidence interval.

All analyses will be undertaken using STATA 15 (StataCorp, USA).

### *Secondary outcomes*

The secondary outcome measures will be 30-day mortality and hospital length of stay. We will use univariate logistic regression and present crude 30-day mortality (dependent variable) rates for patients with or without post-operative infection (independent variable). Secondary outcomes will be analysed using the same approach as the primary outcome. Analyses will also be repeated for each infection type. Forest plots comparing mortality for each infection type will be presented to show each OR with 95% CI. We will report rates of different treatments for post-operative infectious

complications by type of infection. We will test association between infection and hospital length of stay using a mixed effects linear regression model and present these in the supplementary material.

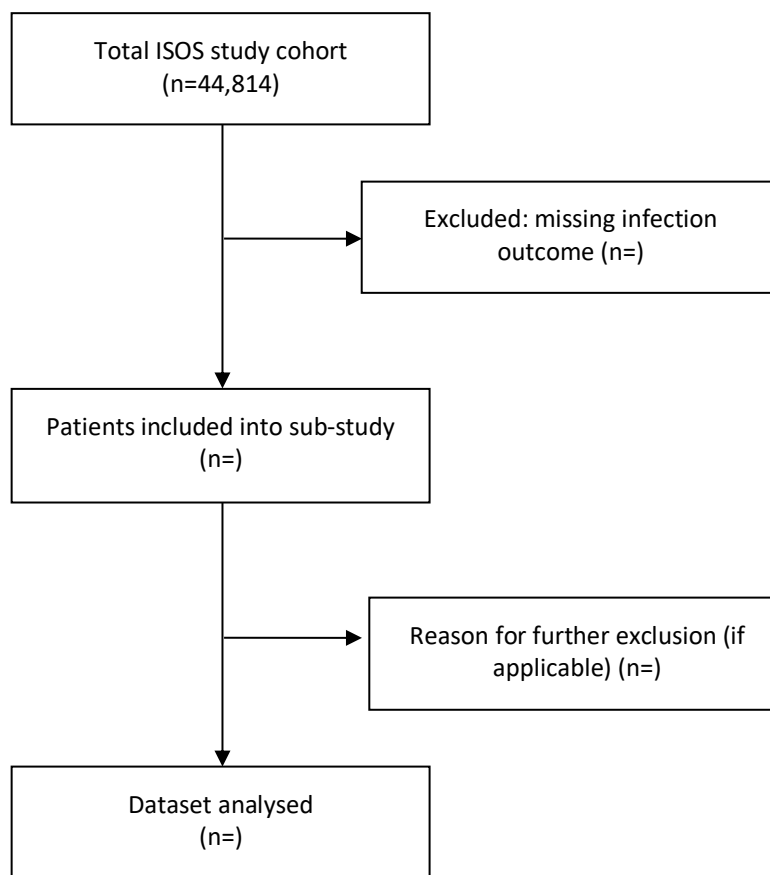
## References

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## Figures and tables

Figure 1. STROBE flow diagram of study population



**Table 1. Baseline patient characteristics.**

All data presented as n (%) unless specified otherwise. ASA, American Society of Anesthesiologists physical status score; COPD, chronic obstructive pulmonary disease.

	All patients n=44814	Patients with infection n=	Patients without infection n=
Age in years (mean SD)			
Age in years (median range)			
Male			
Smoker			
<b>ASA score</b>			
I			
II			
III			
IV			
<b>Co-morbid disease</b>			
Coronary artery disease			
Heart failure			
Diabetes mellitus			
Cirrhosis			
Metastatic cancer			
Stroke			
COPD / asthma			
Other			
<b>Most recent result before surgery</b>			
Haemoglobin g/L (median range)			
Leukocytes x10 <sup>9</sup> /L (median range)			
Sodium mmol/L (median range)			
Creatinine µmol/L (median range)			
<b>Anaesthetic technique</b>			
General			
Spinal			
Epidural			
Sedation/Local			
<b>Surgical procedure</b>			
Orthopaedic			
Breast			
Obstetrics and gynaecology			
Urology and kidney			
Upper gastro-intestinal			
Lower gastro-intestinal			
Hepato-biliary			
Vascular			
Head and neck			
Plastics and cutaneous			
Cardiac			
Thoracic			
Other			
<b>Severity of surgery</b>			
Minor			
Intermediate			

Major			
<b>Other measures</b>			
Laparoscopic surgery			
Cancer surgery			
Use of surgical checklist			
Critical care immediately after surgery			

**Table 2. Infection after surgery.**

Univariate (unadjusted) and multivariable (adjusted) logistic regression models for development of post-operative infection. Data presented as odds ratios and 95% confidence intervals (CI). ASA, American Society of Anesthesiologists physical status score; COPD, chronic obstructive pulmonary disease.

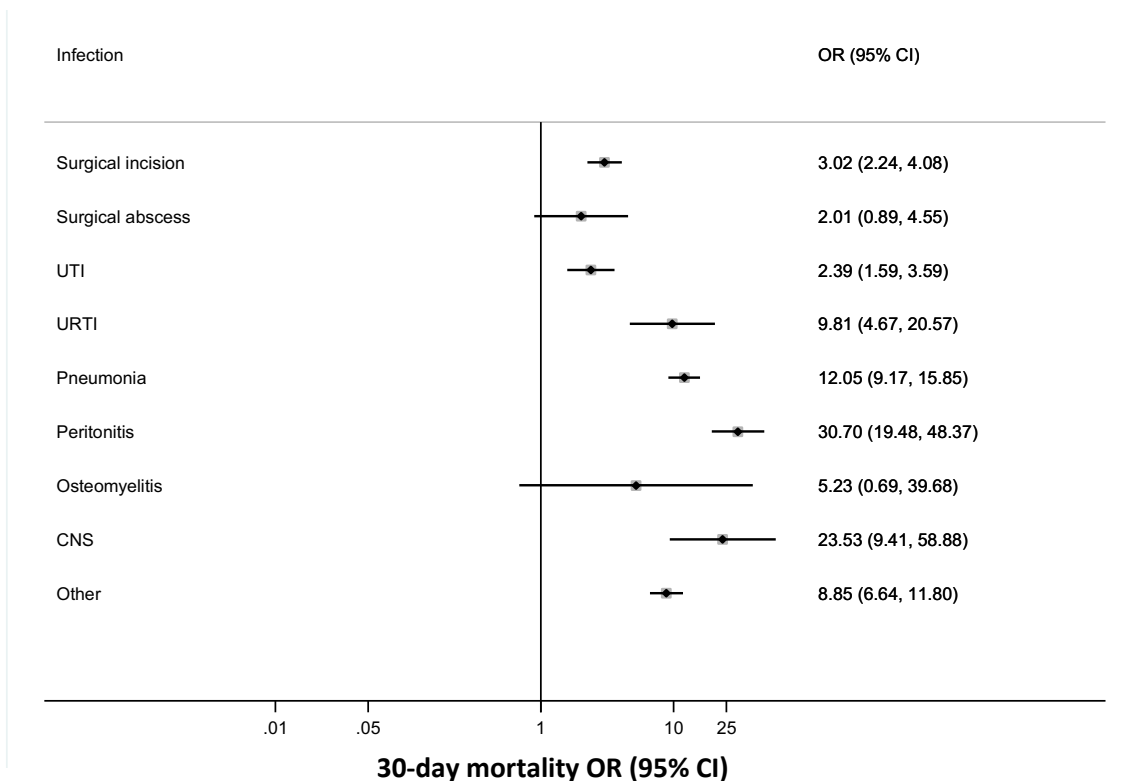
	Infection n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Age		---	---	---
Male				
Current smoker				
<b>ASA score</b>				
I		Reference	---	---
II				
III				
IV				
<b>Co-morbidity</b>				
Coronary artery disease				
Heart failure				
Diabetes mellitus				
Cirrhosis				
Stroke				
COPD/Asthma				
Other				
<b>Surgical procedure</b>				
Orthopaedics				
Breast				
Obstetrics and gynaecology				
Urology & kidney				
Upper gastro-intestinal				
Lower gastro-intestinal				
Hepato-biliary				
Vascular				
Head and neck				
Plastics and cutaneous				
Cardiac				
Thoracic				
Other				
<b>Severity of surgery</b>				
Minor		Reference	---	---
Intermediate				
Major				
<b>Other measures</b>				
Laparoscopic surgery				
Cancer surgery				
Use of surgical checklist				

**Table 3. Post-operative infections and mortality.**

Data presented as n (%). Some patients may have developed more than one complication, and consequently in some cases the denominator is the number complications whilst in the left most column the denominator is the number of patients. The cell at the bottom of the far right column represents the number of deaths divided by the number of patients with at least one complication. Univariate (unadjusted) and multivariable (adjusted) logistic regression models for development of post-operative infection for each type and total number of infections. Adjusted variables include patient characteristics and anaesthetic and surgical factors used in primary analyses. Data presented as odds ratios and 95% confidence intervals (CI).

	n	Severity of complications			Mortality	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
		Mild	Moderate	Severe				
<b>No infection</b>		-	-	-		-	-	-
<b>Infection</b>								
Superficial surgical site	1320 (2.9)	681/1320 (51.6)	517/1320 (39.2)	122/1320 (9.2)	17/1320 (1.3)			
Deep surgical site	566 (1.3)	120/566 (21.2)	250/566 (44.2)	196/566 (34.6)	28/566 (4.9)			
Body cavity	340 (0.8)	97/340 (28.5)	136/340 (40.0)	107/340 (31.5)	24/340 (7.0)			
Pneumonia	708 (1.6)	240/708 (33.9)	325/708 (45.9)	143/708 (20.2)	55/708 (7.8)			
Urinary tract	681 (1.5)	294/681 (43.2)	333/681 (48.9)	54/681 (7.9)	13/681 (1.9)			
Bloodstream	417 (0.9)	140/417 (33.6)	162/417 (38.8)	115/417 (27.6)	48/417 (11.5)			
Total	4032	1572/4032 (39.0)	1723/4032 (42.7)	737/4032 (18.3)	104/4032 (2.6)			

**Figure 2. Forest plots showing the odds ratios for 30-day mortality for different types of infection. (Example)**



**Table 4. Effect of post-operative infection on hospital length of stay.**

Univariate (unadjusted) linear regression models for hospital length of stay in days. Data presented as mean (SD) with beta coefficients and 95% confidence intervals (CI).

	Hospital length of stay		
	Mean (SD)	$\beta$ coefficient (95% CI)	p-value
No infection		-	
<b>Infection</b>			
Superficial surgical site			
Deep surgical site			
Body cavity			
Pneumonia			
Urinary tract			
Bloodstream			
Total			

## Supplementary Figure S2. Paper case record form (CRF) for International Surgical Outcomes Study.

Patient name: .....

Date of birth: dd/mm/yyyy

**International Surgical Outcomes Study Case Record Form v2.3**

For use with Outcomes definitions guide

Age  years      Gender  M  F      Current smoker  Y  N  
 ASA  I  II  III  IV      Black ethnicity (eGFR)  Y  N

Chronic Disease (*tick all that apply*):

Coronary Artery Disease       Heart Failure  
 Diabetes Mellitus       Cirrhosis  
 Metastatic cancer       Stroke  
 COPD / Asthma       Other

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

Haemoglobin  g/L      Leucocytes  x10<sup>9</sup>/L  
 Sodium  mmol/L      Creatinine  μmol/L

Anaesthesia induction time &amp; date:

H	H	m	m	D	D	0	M	2	0	1	4
---	---	---	---	---	---	---	---	---	---	---	---

Anaesthetic technique (*tick all that apply*)

General       Spinal       Epidural       Sedation / Local

Surgical procedure category (*single best answer*):

Orthopaedic       Breast  
 Obstetrics & Gynaecology       Urology & Kidney  
 Upper gastro-intestinal       Lower gastro-intestinal  
 Hepato-biliary       Vascular  
 Head and neck       Plastics / Cutaneous  
 Cardiac       Thoracic (lung & other)  
 Thoracic (gut)       Other

Severity of surgery       Minor       Intermediate       MajorLaparoscopic surgery       Y       NCancer surgery       Y       NSurgical checklist used (eg WHO checklist)       Y       NCritical care immediately after surgery       Y       N

Data entry staff use only

ISOS patient Identifier: 

Patient name: .....

Date of birth: dd/mm/yyyy

**Outcome after surgery**

**Infection**

- Superficial surgical site    Mild     Moderate     Severe     None
- Deep surgical site    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
- Stroke    Mild     Moderate     Severe     None
- Cardiac arrest    Severe     None

**Other**

- Gastro-intestinal bleed    Mild     Moderate     Severe     None
- Acute kidney injury    Mild     Moderate     Severe     None
- Post-operative bleed    Moderate     Severe     None
- ARDS    Mild     Moderate     Severe     None
- Anastomotic leak    Mild     Moderate     Severe     None
- Other    Mild     Moderate     Severe     None

**Treatment for post-operative complications:**

- Drug therapy, blood transfusion or parenteral nutrition     Y     N
- Surgical or radiological procedure     Y     N
- Critical care admission     Y     N

Hours in Post-Anaesthetic Care Unit after surgery

h	h
---	---

Days in critical care after surgery

d	d
---	---

Days in hospital after surgery

d	d
---	---

Status at 30 days after surgery     Alive     Dead

**Data entry staff use only**

ISOS patient Identifier:

