International Surgical Outcomes Study (ISOS)

International observational cohort study of complications following elective surgery

Study protocol version 1.0

23rd September 2013

Short title	*ISOS study*
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UK Research ethics committee reference	*13/YH/0371*
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Study website	www.isos.org.uk

1. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 1.0, dated 23rd September 2013)**, 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.

Chief investigator name: Rupert Pearse

Chief investigator site: Barts Health NHS Trust

Signature and date: Rupert Pearse **23rd September 2013**

Principal Investigator Agreement

The clinical study as detailed within this research protocol **(Version 1.0, dated 23rd September 2013)**, 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:

Principal Investigator Site:

Signature and Date:

2. SUMMARY/SYNOPSIS

Short title	ISOS study
Methods	International, 7-day observational cohort study of complications following elective surgery
Research sites	Hospitals undertaking elective surgery worldwide
Objective	To provide detailed data describing post-operative complications and associated mortality
Number of patients	Not specified. All eligible patients undergoing surgery during the study week.
Inclusion Criteria	All adult patients (aged ≥18 years) undergoing elective surgery during the 7 day study period with a planned overnight stay
Statistical analysis	Univariate analysis will be used to test factors associated with surgical complications, admission to critical care 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.
Proposed Start Date	A seven day period between April and June 2014
Proposed End Date	Data collection will end by August 2014
Study Duration	Four months

3. INTRODUCTION

Over 230 million patients undergo surgery worldwide each year with reported hospital mortality between 1 and 4%.[1-3] Complications following major surgery are a leading cause of morbidity and mortality.[4-9] In the overall 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.[7, 8] Patients who develop complications but survive to leave hospital often suffer reductions in functional independence and long-term survival.[4-6] 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.[4] Data from the National Surgical Quality Improvement Programme in the USA suggests that survival amongst patients who develop post-operative complications varies between hospitals, suggesting both the potential and need to improve clinical outcomes in this population.[10] 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.[11]

A recent study provided the first report of post-operative outcomes at a European level (EuSOS).[2] 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 post-operative complications and associated mortality.

4. STUDY OBJECTIVES

Primary objective

To confirm the incidence of 30-day in-hospital complications following elective in-patient surgery.

Secondary objectives

1. To confirm the 30-day in-hospital mortality associated with these complications
2. To describe the relationship between critical care admission and post-operative complications
3. To describe the effect of post-operative complications on duration of hospital stay

5. METHODS

International, observational, 7-day cohort study. Each national group will select a single seven-day period for patient recruitment between April and June 2014.

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

Exclusion Criteria: Patients undergoing emergency surgery, planned day-case surgery or radiological procedures.

6. STUDY PROCEDURES

Consent procedures

The requirement for patient consent will vary according to regulations in the participating nations. During the European Surgical Outcomes Study (EuSOS), which used identical methods of data capture, investigators were required to take written informed consent in only one of 28 nations. We anticipate that patient consent will not be required most nations taking part in ISOS 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 ISOS 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 ISOS 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 ISOS 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 surgery during the study week. 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

ISOS 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 ten centres from any country will be required for participation and only centres including 20 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 20 valid patients will be excluded in the data analysis. Data will be presented in 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. No comparison will be made between individual nations and 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, admission to critical care 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.

Primary outcome measure

In-hospital post-operative complications of any cause (censored at 30 days following surgery).

Secondary outcome measures

- In-hospital all-cause mortality (censored at 30 days following surgery)
- Admission to critical care (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.

8. SAFETY CONSIDERATIONS

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

9. 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. ISOS 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 ISOS 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.

10. SAFETY REPORTING

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

11. MONITORING & AUDITING

ISOS study master documents will be audited by the sponsor 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 ISOS study team will not routinely monitor data collection in individual hospitals or conduct source data verification.

12. TRIAL COMMITTEES

Trial Management Group

The ISOS trial will be managed by the Adult Critical Care Research team based at Queen Mary University of London. The day-to-day conduct of the trial will be led by the trial management group, chaired by Rupert Pearse.

Trial Steering Committee

The trial steering committee will be appointed with an independent chairperson, lay representation and independent members. There is no role for a Data Monitoring Committee.

13. FINANCE AND FUNDING

The ISOS study is funded by an unrestricted research grant from Nestlé Health Science SA. The funder will play no role in study design, conduct, data collection, data analysis, reporting or interpretation of the results.

14. INDEMNITY

The ISOS study is sponsored by Queen Mary University of London who has appropriate indemnity arrangements in place.

15. 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. ISOS 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 ISOS data prior to submission. In the event of disagreement within the steering committee, the chief investigator will make a ruling. Any analysis incorporating ISOS 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, Queen Mary University of London, 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 ISOS 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 ISOS project.

16. REFERENCES

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7. Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, Pearse RM. Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. Anaesthesia. 2008; **63**(7): 695-700.

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17. Example Case Record Form

Age ☐☐☐ years Gender ☐ M ☐ F Current smoker ☐ Y ☐ N

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
- ☐ Other

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

Haemoglobin ☐☐☐.☐ g/L Leucocytes ☐☐.☐ x10^9/L

Sodium ☐☐☐ mmol/L Creatinine ☐☐☐.☐ µmol/L *

Anaesthesia induction time & date: H H m m D D M M 2 0 1 4

Anaesthetic technique (tick all that apply):

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

Surgical procedure category (*single* best answer):

- ☐ Orthopaedic
- ☐ Breast
- ☐ Gynaecological
- ☐ Obstetric
- ☐ Upper gastro-intestinal
- ☐ Lower gastro-intestinal
- ☐ Hepato-biliary
- ☐ Vascular
- ☐ Urology and Kidney
- ☐ Head and neck
- ☐ Cardiac
- ☐ Plastics / Cutaneous
- ☐ Thoracic (oesophagus)
- ☐ Thoracic (lung & other)

Surgical checklist used (e.g. WHO checklist): ☐ Y ☐ N

Laparoscopic surgery: ☐ Y ☐ N

Cancer surgery: ☐ Y ☐ N

Severity of surgery: ☐ Minor ☐ Major ☐ Intermediate

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** ☐

Critical care admission any time during hospital stay? ☐ **Y** ☐ **N**

If yes, day of critical care admission (day 0=day of surgery): d d

If yes, duration of critical care stay (days): d d

Duration of hospital stay after surgery (days): d d

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