VISION-UK Study 2 statistical analysis plan 1.0 14 May 2018

**ChronoVISION-UK**

**Statistical Analysis Plan – study 2: timing of surgery and risk of postoperative morbidity: Version 1.0**

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# Background

Over 230 million patients undergo surgery worldwide each year with reported hospital mortality between 1 and 4%.1 Complications following major surgery are a leading cause of morbidity and mortality, of which myocardial injury is particularly common occurring in around 25% patients (as measured using high-sensitivity troponin assays).2,3 Coronary artery disease, as quantified preoperatively by CT angiogram, does not appear to be account for the majority of perioperative myocardial injury.4 This suggests that other mechanisms may contribute to cardiac morbidity.

Endogenous circadian rhythms regulate brain, autonomic nervous system, immune and cardiovascular physiology.5 Dysregulated circadian patterns are potentially deleterious in individuals susceptible to adverse cardiovascular events. The occurrence of stroke, myocardial infarction, and sudden cardiac death are strikingly more frequently in the morning.6 In heart failure, autonomic dysfunction is common and is linked to chronic disruptions of the circadian clock that exacerbate contribute to cardiovascular risk.7 These observations extend to cardiac surgery, although as yet no studies have explored this hypothesis in noncardiac surgery.8 Excess cardiovascular risk after noncardiac surgery also appears to be associated with systemic inflammation, which in turn is dysregulated by loss of circadian homeostasis.9,10

VISION-UK is a national prospective cohort study designed to assess the relationship between timing of operation and post-operative myocardial injury, as measured by high-sensitivity plasma troponin, other complications and mortality in adult patients following elective surgery. The anticipated sample size is ~4200 patients from 4 different UK hospitals. 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 VISION-UK study of the relationship between timing of surgery and postoperative morbidity, including myocardial injury. 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.

# Aim

To demonstrate the relationship between timing of surgery and risk of postoperative morbidity.

# Objectives

The primary outcome measure of this study will be morbidity free days within the first 7 days of surgery, as defined by the Post Operative Morbidity Survey.

# Initial descriptive analysis

## 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-style flow diagram. The inclusion criteria are all adult patients (age≥45 years) undergoing elective surgery in a participating hospital with a planned overnight stay. Patients undergoing 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. 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 NCSS 11.

 Handling of missing data is outlined in section 6.0.

## 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, gender, body mass index, ethnicity, smoking status and American Society of Anesthesiologists (ASA) Physical Status grade.

 Surgery related: Surgical procedure, laparoscopic surgery, cancer surgery, severity and duration of surgery.

 Co-morbidities: Coronary artery disease, Heart failure, Diabetes mellitus (insulin treated), Diabetes mellitus (non-insulin treated), metastases, cirrhosis, cerebrovascular disease, transient ischaemic disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease.

 Pre-operative blood test results: haemoglobin, leucocytes (including differential), plasma sodium and other electrolytes.

# Primary analysis

The primary outcome measure of this study will be morbidity free days within the first 7 days of surgery, as defined by the Post Operative Morbidity Survey. The principal exposure will be comparing outcomes in patients with surgery commencing in the morning (defined as 0800-1300h) to patients undergoing surgery in the afternoon (defined as 1300-1900h). The primary effect estimate will be the odds ratio of POMS-defined morbidity, reported with 95% confidence intervals and p-value (Table 2). The significance level will be set at p<0.05. To adjust for potential confounding, a multivariable logistic regression model will be constructed, including all biologically plausible predictor variables. With the expected large sample size, a large number of predictors can be included in the model without compromising statistical power, thus predictors will be selected based on clinical suitability and assessment of correlated variables. The model will be adjusted for the following covariates: age, gender, smoking status, surgical procedure category and duration, ASA grade, presence of co-morbidities, anaesthetic technique, laparoscopic and cancer surgery). All predictors will be entered into the model using forced simultaneous entry.11 The results of the regression models will be reported as odds ratios with 95% confidence intervals and associated p-values (Table 2). Unadjusted odds ratios will also be presented for comparison in a supplementary file. 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 and will be assessed using the Variance Inflation Factor (VIF) as required. A VIF>10 will be considered to be collinear and will be excluded from the analysis.

# Secondary analyses

## Individual domains of the Post Operative Morbidity Survey within the first 7 days of surgery.

The primary analysis will be repeated defining the outcome according to individual domains of the Post Operative Morbidity Score.

## Clavien-Dindo defined complications.

Data required to classify complications within 30 days of surgery according to the Clavien-Dindo grading system will also be presented, which provides information on the severity of postoperative morbidity. The number and percentage of patients in each Clavien-Dindo grade will be reported (Table 5). 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.

## Myocardial injury:

Defined by raised plasma troponin >14ng/l following in-patient surgery.

The primary analysis will be repeated replacing postoperative myocardial injury within 3 days after surgery as the outcome.

## 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 6). 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 of critical care free days will also be presented, but will not be subjected to any statistical tests (Table 6).

## Post-operative mortality

The number and percentage of deaths within 30 days of surgery will be reported for each NLR category. 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.

# Handling of missing data

## 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. If ≤10% of data is missing at random (MAR), then a complete case analysis will be conducted by excluding patients with missing data. If ≥10-25% 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. IF >25% of data are missing then this will handled by list-wise deletion. If data for any particular site are completely missing, then the site will be excluded from the analysis.

## 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. Dummy tables and figures

## Figure 1: Flow diagram

Total VISION-UK study cohort (n)

Reason for exclusion (n)

Patients with data available for inclusion into sub-study (n)

Reason for exclusion (n)

Dataset analysed (n): Time of surgery AM/PM

## Figure 2: Kaplan meier plot for time to become morbidity free within first 7 days of surgery, stratified by time of surgery (AM/PM).

## Figure 3: Kaplan meier plot for length of hospital stay (adjusted for death), stratified by time of surgery (AM/PM).

## Table 1: Baseline characteristics.

|  |  |  |
| --- | --- | --- |
| All patients  (n%) | AM (n%) | PM (n%) |
| Age (mean, SD) | | |
| Gender (%male) | | |
| Smoker | | |
| Ethnicity | | |
| RCRI | | |
| POSSUM | | |
| |  |  |  | | --- | --- | --- | | Atrial fibrillation |  |  | | Congestive heart failure |  |  | | Coronary artery disease |  |  | | Cerebral vascular event |  |  | | Obstructive sleep apnoea |  |  | | Peripheral vascular disease |  |  | | HTN |  |  | | COPD |  |  | | Diabetes |  |  | | Active cancer |  |  | | Haemoglobin |  |  | | CKD |  |  | | | |
| ASA grade | | |
| I | | |
| II | | |
| III | | |
| IV | | |
| Severity of surgery | | |
| Minor | | |
| Intermediate | | |
| Major | | |
| Duration of surgery | | |
| Fluids during surgery | | |
| Blood loss during surgery | | |
|  | | |
| Surgical Procedure category | | |
| Orthopaedic | | |
| Breast | | |
| Thoracic | | |
| Obstetrics & Gynaecology | | |
| Upper gastro-intestinal | | |
| Lower gastro-intestinal | | |
| Hepato-biliary | | |
| Vascular | | |
| Urology & Kidney | | |
| Head & Neck | | |
| Leukocyte counts | | |
| White cell count | | |
| Neutrophil (n;%) | | |
| Lymphocyte (n;%) | | |
| Monocyte (n;%) | | |
| Basophil (n;%) | | |
| Eosinophil (n;%) | | |
| Haemoglobin | | |
| Platelets (n) | | |

## Table 2

Multivariable logistic regression models for development of post-operative morbidity: data presented as n (%), odds ratios and 95% confidence intervals (CI).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Postop morbidity n (%) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | p value |
| Age in years (mean SD) |  |  |  |  |
| Male |  |  |  |  |
| Frailty |  |  |  |  |
| Current smoker |  |  |  |  |
| BMI (mean SD) |  |  |  |  |
| *Co-morbidities* | | | | |
| Atrial fibrillation |  |  |  |  |
| Congestive heart failure |  |  |  |  |
| Coronary artery disease |  |  |  |  |
| Cerebral vascular event |  |  |  |  |
| Obstructive sleep apnoea |  |  |  |  |
| Peripheral vascular disease |  |  |  |  |
| HTN |  |  |  |  |
| COPD |  |  |  |  |
| Diabetes |  |  |  |  |
| Active cancer |  |  |  |  |
| Haemoglobin |  |  |  |  |
| CKD |  |  |  |  |
| *Urgency of surgery* | | | | |
| Elective |  |  |  |  |
| Emergency |  |  |  |  |
| *Type of surgery* | | | | |
| Vascular |  |  |  |  |
| General |  |  |  |  |
| Thoracic |  |  |  |  |
| Major urology or gynaecology |  |  |  |  |
| Major orthopaedic |  |  |  |  |
| Major neurosurgery |  |  |  |  |
| Other |  |  |  |  |
| *Surgical technique* | | | | |
| Endoscopic |  |  |  |  |
| Open |  |  |  |  |
| *Preoperative Leukocyte count* |  |  |  |  |
| Neutrophil |  |  |  |  |
| Lymphocyte |  |  |  |  |
| Monocyte |  |  |  |  |
| Basophil |  |  |  |  |
| Platelets |  |  |  |  |

## Table 3: Cardiovascular complications:

## AM/PM timing of surgery and postoperative troponin rise

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | AM | PM | Odds ratio | P value |
| Troponin rise |  |  |  |  |
| Absolute troponin rise |  |  |  |  |
| Any cardiovascular morbidity |  |  |  |  |
| Myocardial infarction |  |  |  |  |
| Myocardial ischaemia |  |  |  |  |
| Hypotension |  |  |  |  |
| Arrhythmias |  |  |  |  |
| Cardiogenic pulmonary oedema |  |  |  |  |

## Table 4: Outcomes after surgery- POMS-defined morbidity.

# Each domain will include individual sub-components.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | DAY 3 |  | DAY 7 |  |
|  | AM | PM | AM | PM |
| Infection |  |  |  |  |
| Pulmonary |  |  |  |  |
| Renal |  |  |  |  |
| Gastrointestinal |  |  |  |  |
| Wound |  |  |  |  |
| Neurological |  |  |  |  |
| Haematology |  |  |  |  |
| Pain |  |  |  |  |

## 

## Table 5: Outcomes after surgery- Clavien-Dindo grading

Presented for AM/PM; (n;%)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Any c/v complication** |  | **C-D I** |  | **C-D II** |  | **C-D III** |  | **C-D IV** |  | **C-D V** |  |
|  | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| Any C/V event |  |  |  |  |  |  |  |  |  |  |  |  |
| Myocardial infarction |  |  |  |  |  |  |  |  |  |  |  |  |
| Arrhythmia |  |  |  |  |  |  |  |  |  |  |  |  |
| Pulmonary oedema |  |  |  |  |  |  |  |  |  |  |  |  |
| Pulmonary embolism |  |  |  |  |  |  |  |  |  |  |  |  |
| Stroke |  |  |  |  |  |  |  |  |  |  |  |  |
| Cardiac arrest |  |  |  |  |  |  |  |  |  |  |  |  |
| Infectious complications |  |  |  |  |  |  |  |  |  |  |  |  |
| Other |  |  |  |  |  |  |  |  |  |  |  |  |

## 

## Table 6: Post-operative hospital measures

Presented for AM/PM timing of surgery

|  |  |
| --- | --- |
|  | Number of patients |
| Hospital stay for all patients |  |
| Hospital stay for patients with a complication |  |
| Hospital stay for patients who died |  |
| Critical care free days |  |

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