VISION-UK Study 3 statistical analysis plan 1.0 14 May 2018

**Statistical Analysis Plan – study 3: intra-arterial monitoring 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).1-4

Close monitoring of the cardiovascular system is a basic tenet of modern anaesthesia. Despite a range of technologies available, there is surprisingly little evidence that closer monitoring translates to reduced perioperative complications. Although observational studies of preoperative echocardiocardiography and cardiopulmonary exercise testing 2 indicate an association with poorer perioperative outcomes, these findings suggest that clinicians can identify patients most at risk preoperatively. By contrast, prospective studies exploring whether intraoperative monitoring modalities may be associated with reduced postoperative morbidity are lacking. The most amenable parameter for rapid intervention blood pressure, the correction of which is presumably more likely when intra-arterial monitoring is undertaken. Although hypotension is associated with worse outcomes, the impact of interventions to reverse lower blood pressure on postoperative morbidity has been highly variable3,4 and has not included prospective assessment of myocardial injury. The potential additional benefit of other monitors (central venous catheters, cardiac output monitoring) is also unclear.

VISION-UK is a national prospective cohort study designed to assess the relationship between intraoperative arterial blood pressure monitoring 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 use of intra-arterial cardiovascular monitoring and risk of perioperative cardiovascular and all-cause morbidity.

# Objectives

The primary objective of this study is the incidence of myocardial injury, as defined by raised plasma troponin >14ng/l following use of perioperative intra-arterial blood pressure monitoring.

# 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, frailty (reflected by extent of multimorbidity,5 low body mass index <18.5kg.m2 and albumin-creatinine ratio6), 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), sodium.

# Primary analysis

The primary outcome of this study is myocardial injury, as defined by raised plasma troponin >14ng/l following in-patient surgery, within 3 days after surgery. The exposure of interest is the use of perioperative intra-arterial blood pressure monitoring, compared to no intra-arterial blood pressure monitoring, The primary effect estimate will be the odds ratio of myocardial injury, 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.7 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, 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. To assess the reliability of our models, bootstrapping will be undertaken. The results of the regression models will be reported with unadjusted, adjusted odds ratios, 95% confidence intervals and associated p-values (Table 2). Unadjusted odds ratios will also be presented for comparison. 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.

# Secondary analyses

## Intra-arterial monitoring, extent and duration of intraoperative hypotension and hypertension

## Clavien-Dindo defined cardiovascular complications.

## Central venous monitoring

Incidence of CVC monitoring in patients with/without arterial line sited, and effect on primary outcome and severity of cardiovascular morbidity.

## Cardiac output monitoring

Incidence of cardiac output monitoring in patients with/without arterial line sited, and effect on primary outcome and severity of cardiovascular morbidity.

## Noncardiac PostOperative Morbidity

Individual domains of the Post Operative Morbidity Survey within the first 7 days of surgery, graded by 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 ≥2 to classify complications as a binary categorical variable. This will provide an understanding of how the findings are affected by the use of a different system of evaluating complications.

## 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 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. Little’s test will be used to investigate the patterns of the missing data. 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. 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): Arterial Monitoring

## Figure 2: Kaplan meier plot for length of hospital stay (adjusted for death), stratified by use of invasive arterial monitoring. Subpanels also shows additive association of CVC and cardiac output monitoring.

## Table 1: Baseline characteristics.

|  |  |  |
| --- | --- | --- |
| All patients (n%)  | Arterial line (n%)  | None (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 |  |  |
| Hypertension |  |  |
| COPD |  |  |
| Diabetes |  |  |
| Active cancer |  |  |
| Haemoglobin |  |  |
| CKD |  |  |

 |
| ASA grade |
| 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  |
| Leukocyte counts |
| White cell count |
| Neutrophil (n;%) |
| Lymphocyte (n;%) |
| Monocyte (n;%) |
| Basophil (n;%) |
| Eosinophil (n;%) |
| Haemoglobin |
| Platelets (n) |

## Table 2: Use of intra-arterial monitoring and cardiovascular morbidity within first three postoperative days (defined by troponin value/POMS).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ART  | NONE | Odds ratio | P value |
| Troponin rise |  |  |  |  |
| Absolute troponin rise |  |  |  |  |
| Any cardiovascular morbidity |  |  |  |  |
| Myocardial infarction |  |  |  |  |
| Myocardial ischaemia |  |  |  |  |
| Hypotension |  |  |  |  |
| Arrhythmias |  |  |  |  |
| Cardiogenic pulmonary oedema |  |  |  |  |

## Table 3: Intra-arterial monitoring, extent and duration of intraoperative hypotension and hypertension

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ART  | NONE | Mean difference (95%CI) | P value |
| Systolic<100 (duration) |  |  |  |  |
| Systolic>160 (duration) |  |  |  |  |

## Table 4: Use of intra-arterial ±central venous catheterisation (CVC) ± cardiac output (CO) monitoring and cardiovascular morbidity (defined by troponin value/POMS).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ART +CVC | ART +CO | ART +CO+CVC | Odds ratio | P value |
| Troponin rise |  |  |  |  |  |
| Absolute troponin rise |  |  |  |  |  |
| Any cardiovascular morbidity |  |  |  |  |  |
| Myocardial infarction |  |  |  |  |  |
| Myocardial ischaemia |  |  |  |  |  |
| Hypotension |  |  |  |  |  |
| Arrhythmias |  |  |  |  |  |
| Cardiogenic pulmonary oedema |  |  |  |  |  |

## Table 5: Arterial monitoring- noncardiac POMS-defined morbidity within 7 days of surgery.

Individual components of each domain will be reported in addition.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | DAY 3 |  | DAY 7 |  |
|  | ART | NONE | ART | NONE |
| Infection |  |  |  |  |
| Pulmonary |  |  |  |  |
| Renal |  |  |  |  |
| Gastrointestinal |  |  |  |  |
| Wound |  |  |  |  |
| Neurological |  |  |  |  |
| Haematology |  |  |  |  |
| Pain |  |  |  |  |

##

## Table 6: Arterial monitoring- Clavien-Dindo grading for cardiovascular complications within 30 days after surgery.

Presented for ART/NONE; (n;%)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Any c/v complication** |  | **C-D I** |  | **C-D II** |  | **C-D III** |  | **C-D IV** |  | **C-D V** |  |
|  | ART | NONE | ART | NONE | ART | NONE | ART | NONE | ART | NONE | ART | NONE |
| Any C/V event |  |  |  |  |  |  |  |  |  |  |  |  |
| Myocardial infarction  |   |  |   |   |   |   |   |   |   |   |   |   |
| Arrhythmia  |   |  |   |   |   |   |   |   |   |   |   |   |
| Pulmonary oedema  |   |  |   |   |   |   |   |   |   |   |   |   |
| Pulmonary embolism  |   |  |   |   |   |   |   |   |   |   |   |   |
| Stroke  |   |  |   |   |   |   |   |   |   |   |   |   |
| Cardiac arrest |   |  |   |   |   |   |   |   |   |   |   |   |

##

## Table 7: Arterial monitoring- Clavien-Dindo grading for non-cardiovascular complications within 30 days after surgery.

Presented for ART/NONE; (n;%)

## Table 8: Post-operative hospital measures.

|  |  |
| --- | --- |
|  | Number of patientsART/NONE |
| 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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