UNIVERSITY OF EDINBURGH

Study Protocol: Cardiac Injury and Anaemia Following Surgery for Fractured Neck of Femur: An Observational Study

Protocol Author: Dr. Michael Gillies

Co-sponsors	University of Edinburgh and NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh University EH16 4TJ
Funder	None
Funding Reference Number	N/A
Chief Investigator	Dr. Michael Gillies
REC Number Scotland:	
UKCRN portfolio ID	Pending
Version Number and Date	2.0 19th December 2016

Coordinating Centre: Royal Infirmary Edinburgh

ABBREVIATIONS

AUC:	Area Under Curve
CAD:	Coronary Artery Disease
CI:	Confidence Interval
CVA:	Cerebrovascular Accident
CVD:	Cerebrovascular Disease
ECG:	Electrocardiogram
ESRF:	End stage renal failure
FEV1:	Forced Expiratory Volume (1 second)
Hb:	Haemoglobin
hsCRP:	Highly Sensitive C-Reactive Protein
HRQoL:	Health Related Quality of Life
IL:	Interleukin
IQR:	Interquartile Range
LV:	Left Ventricle
ICU:	Intensive Care Unit
MACE:	Major Adverse Cardiac Events
MALDI-MS:	Matrix Assisted Laser Desorption Ionization Mass Spectrometry
MI:	Myocardial Infarction
MINS:	Myocardial injury after non-cardiac surgery
POMS:	Postoperative morbidity survey
PVD:	Peripheral Vascular Disease
TIA:	Transient Ischaemic Attack
TnI, TnT:	Cardiac Troponin I, T
WHO:	World Health Organisation

Table of Contents

1. Summary

1.1 Summary

Studies suggest that anaemia is associated with increased rates of complications and death following surgery. Some 2.1 million units of red blood cells are transfused each year in the UK, many in the perioperative period. Blood transfusion is an expensive and finite resource and optimum transfusion threshold in surgical patients is yet to be defined. Patients commonly receive blood transfusions to reduce the risk of myocardial ischaemia or improve perfusion of other organs (e.g. the kidneys), but this treatment may have important adverse effects including postoperative infection. There is great interest in restrictive transfusion practices (e.g. a transfusion trigger of 70 g^{L-1}), however patients with co-existing cardiovascular disease have been excluded from studies of restrictive versus liberal transfusion strategies.

Uncertainty and the need for more evidence is highlighted in recent recommendations from the National Institute of Clinical Excellence (NICE) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI). These recommend a restrictive transfusion practice, using 7$g.dL^{-1}$ as the "default" threshold, but both recommend caution for patients with CVD and NICE made further research in populations with CVD a research priority (1,2). We recently showed that meta-analysis of trial data restricted to populations with CVD (excluding cardiac surgery) indicate higher rates of acute coronary syndrome (ACS) with restrictive practice (RR: 1.78, 95% confidence interval 1.18 to 2.70, P=0.01; NNT ≈50), with substantial uncertainty remaining about mortality.(3) Uncertainty for patients with CVD is also supported by meta-analysis of trial data in cardiac surgery populations.(4) Hence, there is uncertainty if a "restrictive" perioperative transfusion strategy is optimal in the particular setting of cardiovascular disease.

Highly sensitive troponin assays are now available, which allow clinicians to reliably detect cardiac injury in increased numbers of patients who have undergone major surgery. Troponin release after surgery is common, as high as 40% in some studies. Many of these patients do not exhibit classical symptoms and signs of myocardial infarction (MI). Postoperative elevated troponin that does not fulfil standard definitions of MI is referred to as myocardial injury after non-cardiac surgery (MINS). Potential mechanisms for MINS are coronary events due to plaque rupture or coronary artery thrombosis, oxygen supply-demand imbalance or troponin leak resulting from inflammation.

Acute kidney injury (AKI) is also a leading cause of morbidity and mortality following major surgery with an estimated incidence of 10% in undergoing orthopedic surgery. Epidemiological work has identified anaemia as a risk factor for postoperative acute kidney injury (AKI).

Patients undergoing surgery for fractured neck of femur are often elderly, with co-morbidities and a high risk of postoperative complications, including MI and AKI. We propose to conduct a study with the following aims:

1. To describe the incidence of anaemia and transfusion in patients undergoing surgery for fractured neck of femur.
2. To use clinical and biochemical data to measure the incidence of perioperative cardiac and kidney injury in this group.
3. To evaluate highly sensitive serum troponin and urinary MALDI-MS as possible endpoints in a future prospective randomised trial of perioperative transfusion.

1.2 Lay Summary

Many frail and elderly patients undergo surgery for hip fracture every year. Many of these patients have other health problems including heart disease and anaemia ("low blood count) either from chronic illness, bleeding at the time of injury or during subsequent surgery. Many patients will develop complications.

Doctors looking after these patients commonly prescribe a blood transfusion around the time of surgery, which may increase the amount of oxygen the blood can carry and therefore prevent heart attacks. It may also help patients get out of bed more quickly after surgery.

However, blood transfusions can have side effects such as causing heart failure or increasing infections after surgery. These can delay patient recovery too. Although some research has been done in this area, anaesthetists and surgeons are still unsure of when to prescribe blood transfusions to these patients. In particular, we are not sure about how low the blood count should be before a blood transfusion is ordered. Current guidelines suggest that prescribing at a lower haemoglobin count (70 g/L) is better, but there is research which suggests that this level is too low if the patient has a history of heart disease.

We wish to measure the incidence of anaemia, transfusion, heart attacks, kidney damage and other complications in patients undergoing surgery for fractured neck of femur. All patients that

present to our hospital with a broken hip will be able to take part in this study. We will measure heart damage with a blood test that is very sensitive and we will measure kidney damage with a standard blood test and a new urine test. We will also collect data on other complications. This will provide important information to deign a future study looking at the correct transfusion level in the patients.

2. Background

2.1 Perioperative Blood Transfusion

Epidemiological studies suggest that patient co-morbidities, including anaemia, are associated with increased rates of complications and death following surgery. (5) Anaemia may reflect the severity of chronic disease, and may not have a causative relationship with poor outcomes. Despite this, patients commonly receive blood transfusions to increase haemoglobin concentration with the belief that this may improve clinical outcomes. Some 2.1 million units of red blood cells are transfused each year in the UK, many in the perioperative period, and blood transfusion is an expensive and finite resource. Evidence supports generally restrictive haemoglobin (Hb) transfusion triggers, but the optimum transfusion threshold for important sub-groups of surgical patients remains uncertain.

In the absence of major bleeding, perioperative red blood cell transfusions are typically given to improve oxygen delivery to organs and tissues. Clinicians have particular concern about the risk of myocardial ischaemia, especially among patients with cardiovascular disease. Decision-making is also influenced by potential adverse effects ranging from fluid overload to immune-mediated outcomes, such as increased postoperative infection(6) and tumour recurrence.(7) Published research comparing restrictive and liberal transfusion strategies have typically compared a transfusion threshold of 7-8 $g.dL^{1}$ with 9-10 $g.\ dL^{-1}$.(8) Many of these trials excluded patients with co-existing cardiovascular disease (CVD) and those that included this population typically used less restrictive transfusion triggers (usually ≥8$g.\ dL^{-1}$). This reflects concerns over precipitating or exacerbating major adverse cardiac events (MACE) by exposing patients with CVD to anaemia.

2.2. Fractured Neck of Femur

Patients undergoing surgery for fractured neck of femur (NOF) are an ideal population in which to improve evidence for transfusion practice in populations with CVD. First, they are carried out in large numbers (over 65 000 in the year 2015) in a high proportion of NHS

hospitals.(9) Second, patients are typically high risk, elderly, and have co-existing disease including CVD. Third, as this population is elderly there is a high prevalence of pre-existing anaemia, the major risk factor for perioperative blood transfusion. Fourth, fracture-and surgery-associated bleeding result in a high incidence of acute anaemia and high transfusion rates.(10) Finally, there is a high incidence of perioperative mortality, complications (including cardiac complications) and high health/social care resource utilisation, which might be attributable in part to anaemia/transfusion management. In a recent Cochrane review specifically investigating red blood cell transfusion practice in people undergoing surgery for hip fracture, we found low quality evidence in relation to mortality, functional recovery or postoperative morbidity between 'liberal' versus 'restrictive' thresholds.(11) This review included the FOCUS trial, a large clinical trial of restrictive versus liberal transfusion strategy in patients with fractured NOF.(12) Factors limiting the wider applicability of this trial included: the use of a transfusion threshold of 8g.dL^{-1} (or "symptomatic") in the restrictive group, a short period of exposure to anaemia, and the use of a composite primary outcome with a focus on rehabilitation (death or inability to walk at 60 days) rather than informing care in the perioperative period. This trial used clinical reporting of cardiac events and noted a trend to higher rates in the restrictive group (RR 1.65 (95% CI: 0.99 to 2.74)).

2.3 Measurement of myocardial injury.

Troponin is a protein released from myocardial tissue following myocardial damage. In combination with clinical information and electrocardiography it is used routinely to diagnose and rule out myocardial infarction (MI)(13). Modern Troponin assays are able to detect myocardial necrosis with a high degree of precision. There are two measurable cardiac troponins, Troponin T (TnT) and I (TnI). High sensitivity assays have enabled detection of Troponin in non-Acute Coronary Syndrome (ACS) states such as sepsis, pulmonary embolus, anaemia, critical illness (14) and following surgery where it also correlates strongly with outcome. The VISION Group measured postoperative troponin in a large cohort of patients aged 45yrs or older and found that troponin was an independent predictor of 30d mortality. Importantly, isolated elevations in Tn without symptoms or other clinical signs had similar associations with mortality as MI which fulfilled universal definition. Authors defined Myocardial Necrosis After Non-cardiac Surgery (MINS) as "prognostically relevant elevated Troponin within 30 days of non-cardiac surgery which does not fulfil universal definitions for MI". ECG evidence of ischaemia is not necessary for diagnosis. (15). Other studies have demonstrated a high incidence of elevated postoperative troponin level in general surgical

settings, (16–19) in vascular surgery (20,21) and in orthopaedic surgery (22,23). Potential mechanisms for the elevation in troponin seen following surgery include coronary plaque rupture and thrombosis (Type I MI), and oxygen supply/demand imbalance (Type II MI) and possible cellular "leak" due to inflammation. There is uncertainty whether troponin elevation following surgery reflects true myocardial necrosis or is an "inflammation-mediated" phenomenon.(17) Similarly, it is not known whether the association with adverse outcomes is an epiphenomenon, or whether biologically plausible interventions that may decrease myocardial injury can improve patient outcomes. Available evidence strongly supports the hypothesis that more liberal transfusions in "at risk" populations with CVD could reduce Type II MI, which might reduce cardiovascular complications and improve clinical outcomes.(3)

2.4 Measurement of kidney injury.

Current definitions of AKI rely on elevation of serum creatinine, however this typically occurs late in the evolution of renal injury. Currently both the RIFLE and Acute Kidney Injury Network (AKIN) systems exist to classify Acute Kidney Injury.(24) Development of clinically useful early biomarkers of AKI remains elusive. There is an established need for new biomarkers enabling a more accurate and timely detection of acute kidney injury. (25)

Matrix Assisted Laser Desorption Ionization Mass Spectrometry (MALDI-MS) is a novel predictive test of kidney injury which uses urine electrophoresis coupled to a mass spectrometer. Preliminary studies suggest this technique could detect AKI five days earlier than existing biomarkers. Until recently it was a highly specialised research tool, not suitable for clinical practice. However, an early predictive test for AKI based on the analysis of urinary peptide biomarkers by MALDI-MS has now been developed. Such a platform could be for point-of-care detection of AKI in the postoperative setting.

2.5 Current research strategy in this area.

Uncertainty and the need for more evidence is highlighted in recent recommendations from the National Institute of Clinical Excellence (NICE) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI). These recommend a restrictive transfusion practice, using 7g.dL^{-1} as the "default" threshold, but both recommend caution for patients with CVD and NICE made further research in populations with CVD a research priority (1,2). We recently showed that meta-analysis of trial data restricted to populations with CVD (excluding cardiac surgery) indicate higher rates of acute coronary syndrome (ACS) with restrictive practice (RR: 1.78, 95% confidence interval 1.18 to 2.70, P=0.01; NNT ≈50), with substantial uncertainty remaining about mortality.(3) Uncertainty for patients with CVD is also supported by meta-

analysis of trial data in cardiac surgery populations.(4) Hence, there is uncertainty if a "restrictive" perioperative transfusion strategy is optimal in the particular setting of cardiovascular disease.

Consistent with prioritisation by NICE(1) and the NIHR specialty networks (NIHR haematology specialty group HTA priority 2013; topic 20239), we believe that a large randomised trial of transfusion thresholds in a population with high prevalence of CVD and perioperative complications is warranted. Patients undergoing surgery for fractured neck of femur are ideal for such a study. We intend to seek funding for a feasibility study that will lead to an application for a large UK-wide trial (on behalf of the NIAA), which will progress a "precision medicine" approach to the clinical and cost-effective use of blood transfusions. Data provided by this study will be vital to inform such a study.

2.6 Involvement of patients.

A recent research prioritisation exercise was conducted in the field of perioperative medicine by James Lind Alliance partners which included both patients and carers. This identified improving outcomes for patients undergoing emergency surgical care and for elderly patients undergoing surgery as being in the top 10 research questions for this field. Our proposed study fulfils aspects of both these questions.

3 Study Objectives and Experimental Design

3.1 Study Objectives

The objectives of this study is threefold:

1. to measure the incidence of perioperative anaemia and transfusion in patients undergoing surgery for fractured neck of femur.
2. to understand the changes that occur over time in the level of Troponin I in patients undergoing surgery for fractured neck of femur and to answer whether Troponin I can be used in these patients as a real-time marker of myocardial injury. We hope that this will validate the use of Troponin I as the endpoint for a future trial looking at the impact of liberal vs restrictive perioperative blood transfusion in this patient group.
3. to measure the incidence of acute kidney injury in patients undergoing surgery for fractured neck of femur and to evaluate the performance of MALDI-MS against conventional tests of renal function.

3.2 PICO Design

Study design was developed using "Patient Intervention Comparator Outcome" (PICO) method.

Population: We will recruit 200 adult patients undergoing emergency surgery for fractured neck of femur, aged over 50 years.

Intervention: We will use blood samples taken preoperatively and at 24 and 72 hours by the research team or (where able) leftover serum from routinely collected blood samples to minimise need for venepuncture in these patients. We will perform an ECG on the third postoperative day. Urine will be collected at 2 time points post-operatively (within 24 hours and 4-6 days post-operatively).

Comparator: This is an exploratory study in which we are trying to understand the dynamics of serum Troponin I, serum creatinine and urinary MALDI-MS following surgery. We will compare patterns of cardiac and renal injury in anaemic and non-anaemic patients.

Outcome:

Primary: Myocardial injury (based on hsTroponin>Upper reference limit [URL]);

Secondary: Acute Kidney Injury (KDIGO Stage); Urinary MALDI-MS

Other clinical outcomes:

Acute Coronary syndrome (using universal definition)

Mortality (30; 90 days)

POMS score

Infectious complications

Incidence of delirium

Hospital length of stay

Unplanned hospital readmission within 90 days

Health Related Quality of Life (HRQoL) at 90 days (Using "EQ-5D" questionnaire)

Secondary care costs during 90 days post-randomisation

4. Study Objectives

4.1 Objectives

4.1.1 Primary Objective

- To determine prospectively the dynamic changes in Troponin I in patients undergoing surgery for fractured neck of femur

4.1.2 Secondary Objectives

- To estimate the rate of acute kidney injury using Acute Kidney Injury Network (AKIN) Classfication, Serum Creatinine and Urinary MALDI-MS.
- To observe whether changes in Troponin I levels are reflected by electrocardiographic changes via an ECG taken on the 3rd postoperative day.
- To define the clinical diagnosis rate of myocardial infarction according to universal definitions
- To observe rate of transfusion and transfusion trigger
- To estimate the incidence of postoperative complications, in particular infectious complications and delirium.
- To measure hospital length of stay
- To measure 30-day, 90-day and hospital mortality.
- To measure economic and quality of life outcomes

4.2 Endpoints

4.2.1 Primary Endpoint

- Postoperative cTnI

4.2.2 Secondary Endpoints

- Serum creatinine
- Urinary MALDI-MS

4.2.3 Other Clinical Outcomes Collected

- Nadir haemologobin (first 7 days following admission)
- Haemoglobin(Hb) at time of surgery
- Perioperative blood loss
- Number of units transfused
- Blood transfusion rate

- Haemoglobin concentration at blood transfusion
- 30-day major adverse cardiac events
- Myocardial Infarction within 30 days (using universal definition)
- MINS within 30 days
- Mortality (30; 90 days)
- POMS score
- Hospital length of stay
- Unplanned hospital readmission within 90 days
- HRQoL at 90 days
- Secondary care costs during 90 days post-randomisation

5. Study Design

This will be a prospective cohort study. Patients will be consented and then enrolled in the study within 48 hours of hospital admission with fractured neck of femur. Over the intra- and postoperative period, we will collect baseline demographic data, and daily information regarding myocardial infarction, postoperative complications (including death) and blood transfusion.

We will take blood samples for markers of renal and kidney injury preoperatively and at 24 hours and 72 hours following surgery. We will record the results of blood tests that have been routinely taken. Patients will have a point-of-care haemoglobin measurement immediately following surgery in recovery using the “haemocue” system. Urine will be collected at 2 time points post-operatively (within 24 hours and 4-6 days post-operatively).

We will perform a postoperative ECG 72 hours following surgery. We will collect clinical data on postoperative morbidity score (POMS) on day 7, on infectious and cardiac complications prior to hospital discharge. We will also collect economic and quality of life data for up to 90 days following surgery.

6. Study population

Patients aged over 50 years having emergency surgery for fracture neck of femur at the Royal Infirmary Edinburgh.

6.1 Recruitment Rate

The trauma and orthopaedic unit at the Royal Infirmary of Edinburgh perform over 1000 procedures for fractured neck of femur per year and 98% undergo surgical fixation. Based on

published data(12) and UK audit data we expect ≈60% (N = 600) of patients to have cardiovascular co-morbidity. Assuming a recruitment rate of 50%, 300 patients would be potentially recruited in 12 months (7 per week). Assuming a "worst case scenario" of 30% recruitment, we expect to recruit ≈200 patients over 12 months.

6.2 Inclusion Criteria

- Patients with fractured neck of femur.
- Age over 50 years
- Within 48 hours of presentation to the emergency department
- Patients who have consented to take part in the study

6.3 Exclusion Criteria

- Age under 50 years
- Refusal of consent

7. Participant Selection and Enrolment

7.1 Identifying participants

Patients will be identified in the emergency department, on orthopaedic wards or from operating lists. The research team will approach the potential participant or their next of kin (if patient lacks capacity) either in person or by telephone to discuss involvement in the study. If interested in participating, the appropriate information sheet will be provided and a maximum of 24 hours will be given to consider the study and ask any questions. If interested, consent will be sought for inclusion in the study.

7.2 Consent

7.2.1 Obtaining Consent from participants

Patients who are deemed capable of consent by the clinician in charge will be given a patient information leaflet to read which will fully explain the study with its risks and benefits. This will then be discussed with them and consent will be sought by the chief investigator or appropriately trained member of the team.

7.2.2 Consent in the case of incapacity

For most patients admitted to hospital, the case notes have clear information relating to the identity of the guardian/welfare attorney/nearest relative. Contact details for a first contact (and additional contacts) are usually documented in the unitary patient record (a key

document in the patient's medical notes), and/or in the Emergency Department sheet. The patient's guardian/welfare attorney/nearest relative will be identified from this information. No incapacitated patient will be entered into the study without consent from a guardian, welfare attorney or relative. We shall approach the guardian/welfare attorney/nearest relative during a visit to the hospital. He/she will be informed of the nature of the study and given an information sheet and consent form. Should the guardian/welfare attorney/nearest relative consider giving informed consent, he/she will be asked to sign the consent form. Direct consent of these individuals will be preferable, however witnessed phone consent will be acceptable, with the individual signing the consent form at the earliest opportunity. In such cases where telephone consent is obtained, a verbal description of the study will be provided, with an opportunity to ask any questions. This process will be witnessed by a member of the clinical team who is not connected with the study.

7.3 Ineligible and non-recruited participants

A screening log will be maintained of patients eligible but not recruited to the study and the reasons for this.

8. Data Collection

All data will be entered directly onto a secure, trial specific database using REDCap: Research Electronic Data Capture (Vanderbildt University, USA). This is a secure, password protected platform, hosted on University of Edinburgh servers. All identifiable data will be removed before the dataset is extracted for analysis.

The following data will be collected from all participants recruited onto the study:

Preoperative Data

At baseline the following information will be collected:

- date of admission
- Demographic information
- Type of surgery proposed
- Cardiovascular risk factors
- Cardiac medications
- Charleson Comorbidity Index
- Preoperative haemoglobin (Hb)
- Preoperative serum TnI
- Preoperative Creatinine

- Preoperative Urinary MALDI-MS

Intraoperative Data

- Date of surgery
- Type of anesthesia
- Duration of surgery
- Lowest intraoperative Haematocrit (Hct) or Hb measured
- Hb immediately after surgery
- Number of units blood transfused
- Postoperative analgesia
- Postoperative destination (e.g. Ward, Critical Care Unit)

Postoperative Data

First 72 hours postop

- Serum TnI and Creatinine, Hb, urinary MALDI-MS within 24 hours and 4-6 days postoperatively. Where possible blood samples will be timed with existing blood sampling.
- ECG on the 3rd postoperative day
- Transfusion requirement
- Relevant clinical information major adverse cardiac events (MACE) including myocardial infarction.

Hospital Discharge/30 days

- Transfusion requirement
- Length of hospital stay
- MACE
- POMS
- Incidence of Delirium
- Infectious complications
- Mortality 30 days

90 Days

- Emergency readmission
- Mortality
- HRQoL
- Secondary care costs

9. Subgroups

9.1 Anaemia

We will explore cardiac and renal biomarker changes in patients with and without anaemia according to WHO definition and also by current transfusion guidelines. We hope this will inform a study looking at myocardial injury as an endpoint for restrictive versus liberal blood transfusion practice for patients with cardiovascular disease in intensive care. This will enable us to study the range of Troponin values that might occur when the patient becomes eligible for entry to this with a preoperative haemoglobin of 90g/l or less. We will also be able to look at Troponin I levels pre- and post-transfusion. This will not require any further blood samples.

10. Follow up

Patients will be prospectively followed up until hospital discharge by the research team. Hospital records will be checked for hospital mortality by the research team. The research team will access hospital/primary care records for up to 90 days to capture data regarding cardiac events and mortality.

11. Statistics and Data Analysis

11.1 Power

We plan to recruit 200 patients. This is an exploratory study, and not based on a formal power calculation. We propose to recruit for fixed period of 12 months to establish recruitment rates, and provide estimates of the values and distribution of clinical outcomes that will be used to design a full trial. On the admission figures quoted above, 600 patients would be eligible for recruitment each year. Assuming a 50% refusal rate, we could realistically expect to recruit 300 (95% Confidence Intervals [CI] 280-320). Planned recruitment of 200 is well within these limits. We expect 50% of participants to be anaemic, based on previous work. (10)

11.2 Data Analysis

We will report main trial outcomes by anaemic and non anaemic groups. Continuous data will be presented as mean (95% CI), or median (IQR) if non-normally distributed. Binary data will be presented as frequency (%). Parametric and non parametric variables will be compared using appropriate statistical tests.

Exploratory analyses will utilize the hsTnI profiles to define the optimum method for defining myocardial injury in a subsequent trial, for example maximum values, AUC analyses, and proportions exceeding threshold values. Comparisons across the two study groups will be used to explore the possible validity of this measure in a subsequent large transfusion trigger trial, specifically whether differences exist between patients with different haemoglobin profiles during the perioperative period. Other analyses will explore the relative associations between markers of kidney injury, anaemia, and other factors using regression analysis. We will report the proportion of eligible patients, Hb concentration distribution between groups and mean red blood cell use across groups with 95% confident intervals (CI).

11.3 Potential Confounders

Age, sex, socio-economic status, Primary diagnosis, Comorbidities.

Renal failure: This affects Troponin T more than Troponin I (TnI) due to molecular size, but may still affect the elimination of TnI.

Anaemia: Sicker patients are likely to be more anaemic due to sepsis, reduced erythropoietin production and functional iron deficiency. It will therefore be difficult to interpret whether TnI rises are due to anaemia, or due to the critical illness underlying the anaemia. A separate subgroup analysis will be carried out looking at anaemia.

Cardiac medications: the presence of beta-blockers and Angiotensin Converting Enzyme Inhibitors (ACE-I) may affect changes in TnI levels. Certain medications e.g. ACEI may be stopped prior to surgery.

12. Trial management and oversight arrangements

This study will be run in coordination with the Edinburgh Clinical Trials Unit (ECTU).

As this is a purely observational study the likelihood of adverse events is low however we will use ECTU protocols for audit and monitoring.

References

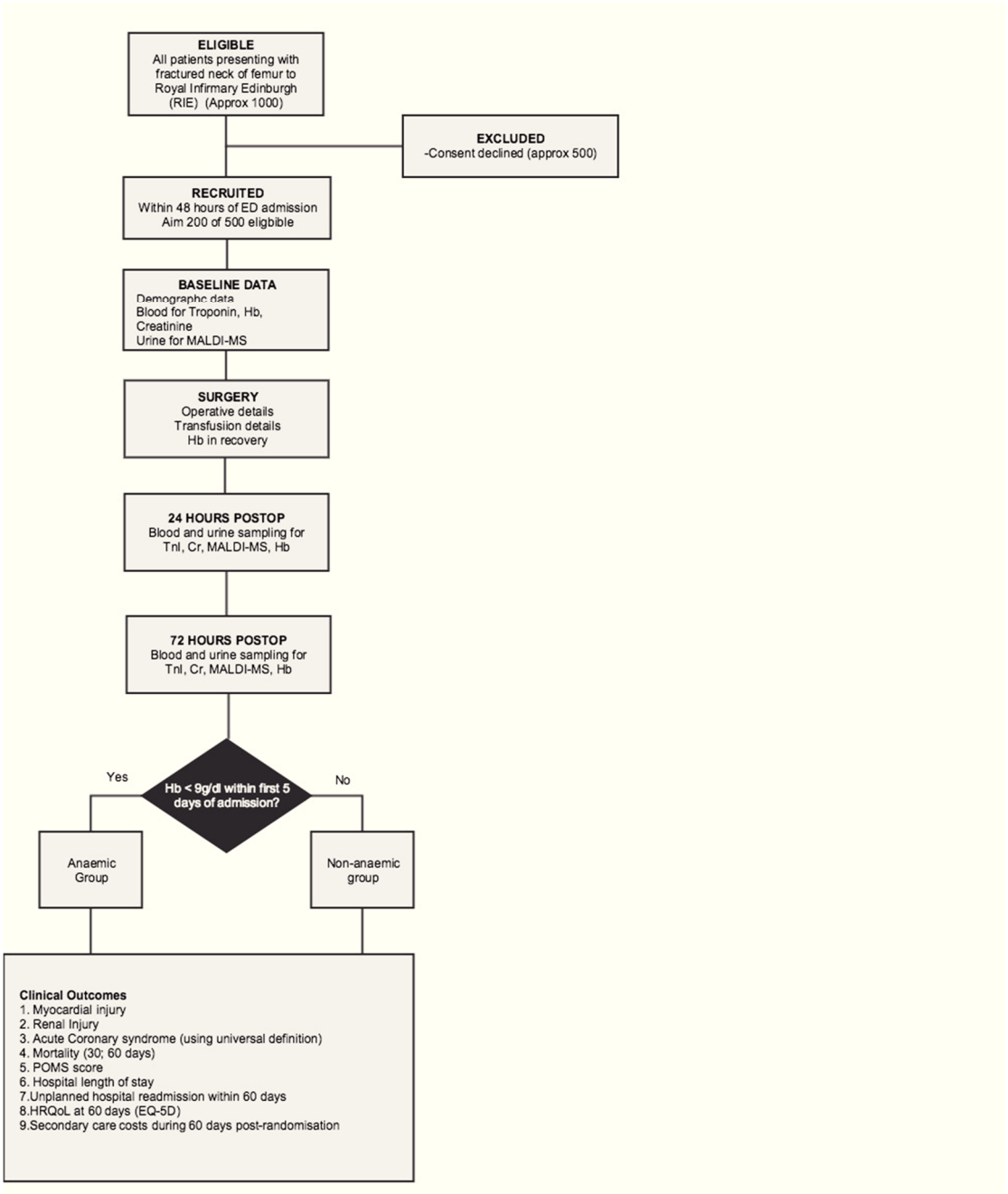
1. Blood transfusion | Guidance and guidelines | NICE. NICE;
2. Klein AA, Arnold P, Bingham RM, Brohi K, Clark R, Collis R, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia. 2016;
3. Docherty AB, O'Donnell R, Brunskill S, Trivella M, Doree C, Holst L, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. Bmj. 2016;i1351.
4. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JAC, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet Haematol. 2015 Dec 17;2(12):e543–53.
5. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. John Wiley & Sons, Ltd; 2015;102(11):1314–24.
6. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ. BMJ Publishing Group Ltd; 2015;350.
7. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg. 2012 Aug;256(2):235–44.
8. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. Massachusetts Medical Society; 1999 Feb 11;340(6):409–17.
9. National Hip Fracture Database (NHFD) annual report 2015 [Internet]. [cited 2016 Apr 19]. Available from: http://www.nhfd.co.uk/nhfd/nhfd2015reportPR1.pdf

10. Kadar A, Chechik O, Steinberg E, Reider E, Sternheim A. Predicting the need for blood transfusion in patients with hip fractures. Int Orthop. Springer; 2013 Feb 5;37(4):693–700.
11. Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, et al. Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane database Syst Rev. 2015 Jan;4:CD009699.
12. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011 Dec 29;365(26):2453–62.
13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2012;60(16):1581–98.
14. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. Eur Heart J. 2011 Mar;32(4):404–11.
15. VISION Group. Myocardial Injury after Noncardiac Surgery. Anesthesiology. 2014;120:564–78.
16. Kavsak PA, Walsh M, Srinathan S, Thorlacius L, Buse GL, Botto F, et al. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: A prospective cohort study. Clin Biochem. 2011;44(12):1021–4.
17. Gillies MA, Shah AS V., Mullenheim J, Tricklebank S, Owen T, Antonelli J, et al. Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. Br J Anaesth. 2015;1–7.
18. Nagele P, Brown F, Gage BF, Gibson DW, Miller JP, Jaffe AS, et al. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. Am Heart J. Mosby, Inc.; 2013 Aug;166(2):325–32.e1.
19. van Waes JAR, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation. 2013 Jun 11;127(23):2264–71.
20. Marston N, Sandoval Y, Zakharova M, Brenes-Salazar J, Santili S, Adabag S, et

al. Troponin elevations following vascular surgery in patients without preoperative myocardial ischemia. South Med J. 2013 Nov;106(11):612–7.

21. Garcia S, Marston N, Sandoval Y, Pierpont G, Adabag S, Brenes J, et al. Prognostic value of 12-lead electrocardiogram and peak troponin I level after vascular surgery. J Vasc Surg. 2013 Jan;57(1):166–72.
22. Chong CP, van Gaal WJ, Profitis K, Ryan JE, Savige J, Lim WK. Electrocardiograph changes, troponin levels and cardiac complications after orthopaedic surgery. Ann Acad Med Singapore. 2013 Jan;42(1):24–32.
23. Hietala P, Strandberg M, Kiviniemi T, Strandberg N, Airaksinen KEJ. Usefulness of troponin T to predict short-term and long-term mortality in patients after hip fracture. Am J Cardiol. 2014 Jul 15;114(2):193–7.
24. Kellum J, Lameire N, for the KDIGO AKI Guideline WG. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204.
25. Honore PM, Jacobs R, Joannes-Boyau O, Verfaillie L, De Regt J, Van Gorp V, et al. Biomarkers for early diagnosis of AKI in the ICU: ready for prime time use at the bedside? Ann Intensive Care. 2012 Jan;2(1):24.
26. Desai SJ, Wood KS, Marsh J, Bryant D, Abdo H, Lawendy A-R, et al. Factors affecting transfusion requirement after hip fracture: can we reduce the need for blood? Can J Surg. 2014 Oct;57(5):342–8.

Appendix A Flow Chart Study Recruitment



Appendix B Postoperative Morbidity Survey (POMS)

Pulmonary	*De novo* requirement for supplemental oxygen or other respiratory support (e.g., mechanical ventilation or CPAP)
Infectious	Currently on antibiotics or temperature >38 °C in the last 24 h
Renal	Presence of oliguria (<500 mL/d), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for a nonsurgical reason
Gastrointestinal	Unable to tolerate an enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting, and abdominal distension
Cardiovascular	Diagnostic tests or therapy within the last 24 h for any of the following: *de novo* myocardial infarction or ischemia, hypotension (requiring pharmacological therapy or fluid therapy >200 mL/h), atrial or ventricular arrhythmias, or cardiogenic pulmonary oedema
Neurological	Presence of a *de novo* focal deficit, coma, or confusion/delirium
Wound complication	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms
Haematological	Requirement for any of the following within the last 24 h: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate
Pain	Surgical wound pain significant enough to require parenteral

Appendix C Complication Definitions

Major Adverse Cardiac Events

Myocardial infarction: Any cardiac ischaemic event fulfilling 3rd Universal Definitions for Myocardial Infarction

Myocardial Injury after Non-cardiac Surgery: Troponin elevation within 30 days of surgery which does not satisfy universal definitions for myocardial infarction.

Arrhythmia: ECG evidence of rhythm disturbance resulting in a fall in mean arterial pressure of greater than 20% or requiring treatment (anti-arrhythmic agents, vasoactive agents, intra venous fluid, etc.).

Cardiac or respiratory arrest: As per UK Resuscitation Council Guidelines.

Cardiogenic pulmonary oedema: Appropriate clinical history and examination with consistent chest radiograph.

Pulmonary embolism: Computed tomography (CT) pulmonary angiogram, clinical or echocardiographic evidence with appropriate clinical history.

Infectious Complications

Infection, source uncertain: Two more of the following associated with strong clinical suspicion of infection (sufficient to require intra-venous antibiotic therapy, etc.):

(i) Core temperature <36C or >38C

(ii) white cell count >12 x 10^9 L^{-1} or <4 x 10^9 L^{-1}

(iii) (iii) respiratory rate >20 breaths per minute or $PaCO^2$ < 4.5 kPa

(iv) (iv) pulse rate >90 bpm

Urinary tract infection: A symptomatic urinary tract infection must meet at least one of the following criteria:

(i) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38C), urgency, frequency, dysuria, or supra-pubic tenderness *and* patient has

a positive urine culture, that is, $>10^5$ microorganisms per cm3 of urine with no more than two species of microorganisms.

(ii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38C), urgency, frequency, dysuria, or supra-pubic tenderness and at least one of the following:

a. Positive dipstick for leucocyte esterase and/or nitrate;

b. Pyuria (urine specimen with >10 WBC mm^{-3});

c. Organisms seen on Gram stain of unspun urine;

d. At least two urine cultures with repeated isolation of the same uro-pathogen with $>10^2$ colonies/ mL in non-voided specimens;

e. $>10^5$ colonies/mL of a single uro-pathogen in a patient being treated with an effective antimicrobial agent for a urinary tract infection;

f. physician diagnosis of a urinary tract infection;

g. physician institutes appropriate therapy for a urinary tract infection.

Other infections of the urinary tract (kidney, ureter, bladder, urethra, etc.): Other infections of the urinary tract must meet at least one of the following criteria:

(i) Patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site.

(ii) Patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathology examination.

(iii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38C), localized pain, or localized tenderness at the involved site and at least one of the following:

a. Purulent drainage from affected site;

b. Organisms cultured from blood that are compatible with suspected site of infection;

c. Radiographic evidence of infection, for example, abnormal ultrasound, computed tomography or magnetic resonance imaging;

d. Physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space;

e. Physician institutes appropriate therapy for an infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space.

Surgical site infection (SSI) (superficial incisional): A superficial SSI must meet the following criteria:

(i) Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following:

a. Purulent drainage from the superficial incision;

b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;

c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative;

d. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Surgical Site Infection (deep incisional):

A deep incisional SSI must meet the following criteria:

i) Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following:

a. Purulent drainage from the deep incision but not from the organ/space component of the surgical site;

b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38C) or localized pain or tenderness, unless incision is culture-negative;

c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathology or radiologic examination;

d. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

An infection that involves both superficial and deep incision sites should be classified as a deep incisional SSI.

Surgical Site Infection (organ/space)

An organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers, which is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection. An example is appendectomy with subsequent sub-diaphragmatic abscess, which would be reported as

an organ/space SSI at the intra-abdominal specific site. An organ/space SSI must meet the following criteria:

i) Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and patient has at least one of the following:

a. Purulent drainage from a drain that is placed through a stab wound into the organ/space;

b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space;

c. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathology or radiologic examination;

d. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Laboratory Confirmed Bloodstream Infection: Laboratory confirmed bloodstream infection must meet at least one of the following criteria:

i) Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.

ii) Patient has at least one of the following signs or symptoms: fever (>38C), chills, or hypotension and at least one of the following:

a. Common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.

b. Common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.

c. Positive antigen test on blood.

Signs and symptoms and positive laboratory results are not to be related to an infection at another site.

Nosocomial pneumonia: Nosocomial pneumonia will be characterized as early or late onset i.e. before or after first 4 days of hospitalisation. Where repeated episodes of nosocomial pneumonia are suspected, a combination of new signs and symptoms and radiographic evidence or other diagnostic testing will be required to distinguish a new episode from a previous one. This category includes ventilator-associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a

tracheostomy or endotracheal tube), however care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia.

Nosocomial pneumonia must meet the following criteria:

i) Two or more serial chest radiographs with at least one of the following:

a. New or progressive and persistent infiltrate;

b. Consolidation;

c. Cavitation.

And at least one of the following:

a. Fever (>38C) with no other recognized cause;

b. Leukopenia (WCC<4 x 10^9 L^{-1}) or leucocytosis (WCC>12 x 10^9 L^{-1})

c. For adults >70 years old, altered mental status with no other recognised cause.

And at least two of the following:

a. New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements

b. New onset or worsening cough, or dyspnoea, or tachypnoea;

c. Rales or bronchial breath sounds;

d. Worsening gas exchange

Appendix D Acute Kidney Injury Classification

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours