The impact of **RES**trictive vers**U**s LIbera**L** **T**ransfusion strategy on cardiac injury and death in patients undergoing surgery for **Hip** Fracture (RESULT-Hip)

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Version No	Date	Summary of Revisions
1.0	25Nov2021	Not implemented
2.0	02Mar2022	• Revision of PISCF in England and Wales to provide further information re: current standard care; clinically significant findings from blood samples ; retention of blood samples for future research; storing data for future research; contacting participants with trial results; 2 optional statements added re post-study data sharing; • Clarifications to protocol re duration of participant involvement and freezer temperature for blood sample storage
3.0	15Sep2022	• inclusion criteria amended to include those who break their hip while an existing inpatient in hospital • addition of a telephone version of the personal consultee declaration form in England, Wales & Northern Ireland (RUK) .
4.0	03May2023	• addition of optional summary A4 information sheets; • introduction of a window for day 1 and day 3 study blood samples • updating of patient information sheets re risks of blood transfusion and rationale for study; minor errors corrected throughout the information sheets. • addition of exclusion criteria - patients with transfusion dependent chronic anaemias • minor clarifications to protocol including assessment and transfusion timelines.

5.0	26Jun2024	• Change to primary outcome from 'death or major adverse cardiac events (MACE) within 30 days of randomisation to 'death OR major adverse cardiac events (MACE) OR new myocardial injury after non cardiac surgery (new MINS) within 30 days of randomisation' • Reduction of sample size from 1964 to 1126 • Extension of recruitment and study end dates by 21 months to 30 April 2026 and 30 April 2027 respectively • Clarification of timelines for : randomisation after qualifying Hb result; blood transfusion after randomisation ; blood transfusion after a subsequent triggering Hb result • Change of wording of exclusion criterion for chronic anaemia for clarification • Addition of advice that all witnesses must be independent • Removal of references to personal legal representatives • Clarification that personal consultees/nearest relatives can ask to withdraw participants from the study • Addition of requirement to collect cause of death from death certificates • Addition of information re a study specific video animation • Update of posters • Other minor clarification and correction of typographical errors • Addition of a document history table to protocol
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SCIENTIFIC ABSTRACT

Design: Multicentre, parallel group randomised controlled clinical and cost effectiveness trial with internal pilot.

Setting: 30 NHS hospitals

Population: Adults aged 60 years or older with hip fracture who become anaemic (Hb ≤ 90 $g.L^{-1}$) from admission until seven days following surgery will be eligible for enrolment and randomisation. Those patients for non-operative management or not expected to survive 48 hours, who have life threatening haemorrhage at the time of screening, pre-randomisation new or suspected acute coronary syndrome , objection to receiving RBC transfusion or chronic anaemias requiring repeated transfusion will be excluded.

Health technologies being assessed: "Liberal" transfusion threshold of ≤Hb 90 $g.L^{-1}$ (target Hb 90-110 $g.L^{-1}$) for duration of acute hospital stay. This is more liberal than some current guidance but consistent with practice of many clinicians in this population.

Control group treatment: "Restrictive" transfusion threshold of ≤75 $g.L^{-1}$ (target of 75-90 $g.L^{-1}$) for duration of acute hospital stay. This is consistent with current NICE guidance. Many clinicians and published reviews note uncertainty and low quality of evidence for this population.

Costs and Outcomes:

The primary outcome will be death OR major adverse cardiac events (MACE) OR new Myocardial Injury after Noncardiac Surgery (new MINS) within 30 days of randomisation. MACE will be defined as any combination of the following: death, myocardial infarction, new arrhythmia, cardiac or respiratory arrest, cardiogenic pulmonary oedema. An ordinal ranking approach will be used in analysis. To maximize validity and consistency, all participants will have troponin measured at randomisation (baseline) and then twice more in days 1 to 5, ideally on the 1st and 3rd calendar days after randomisation with all samples being at least 24h apart from each other. ECGs will be performed at baseline and repeated once in days 2 – 5. Primary outcome will be determined by an expert adjudication team blinded from group allocation.

The *secondary outcomes at 30 days* will be: all-cause mortality, myocardial injury, individual MACE components, new MINS, other complications (acute kidney injury (AKI), infection, delirium); proportion transfused; volume of blood transfused; discharge destination; hospital length of stay; and healthcare related quality of life (HRQoL) using EQ-5D-5L.

The *secondary outcomes at 120 days* will be: all-cause mortality, secondary care costs up to 120 days; HRQoL (EQ-5D-5L), unplanned hospital readmissions within 120 days, mobility, residential status.

Health Economic evaluation: 120-day cost-consequence analysis and long run cost-utility modelling from an NHS and PSS perspective

Process evaluation: We will undertake a process evaluation in the study pilot phase to examine barriers to recruitment and protocol compliance.

Follow up: 120 days post randomisation.

Sample size: 421 per group, giving a total sample size 842 participants (allowing 10% dropout rate). Based on pilot data and expert opinion we expect incidence rate for the primary outcome of death 7%, MACE 10% and new MINS 20% at 30 days and an absolute risk reduction (ARR) of 5% in the primary outcome to be a realistic meaningful effect size that would change practice (33% Relative RR; Number Needed to Treat, 20).

Project time frames: The total project duration is 69 months. In month 1-12 we will undertake approvals, set-up, and 10-site internal pilot. In months 13 – 45 we will set-up the remaining 20 sites. Month 25 – 57 : will be the main recruitment phase. In months 58-69 we will complete follow-up, analysis, report writing.

Expertise: The proposed trial has been developed by an experienced multi-professional team with patient and public involvement throughout.

PLAIN ENGLISH SUMMARY

IMPORTANCE OF PROBLEM

Hip fracture is the most common serious injury in older people. It is the most common reason for older people to need emergency anaesthesia and surgery, and most common cause of death after an accident. More than 95% of these people go on to have surgery. This surgery is often high-risk as patients with hip fracture may already be frail and have other health problems including heart disease and anaemia (low haemoglobin or "low blood count") either from chronic illness, bleeding at the time of injury or during surgery. These patients may be in hospital for a long time and need rehabilitation. Many of them will develop complications, including heart attacks and some will die. Doctors looking after these people commonly prescribe a blood transfusion around the time of surgery. Research suggests that 30-40% of these people have a blood transfusion around the time of operation. These people often already have anaemia before surgery and lose more blood during their operations.

POTENTIAL RISKS AND BENEFITS

A benefit of blood transfusion is that it may increase the amount of oxygen the blood can carry. One reason doctors prescribe blood around the time of surgery is to prevent heart attacks, which can occur if the heart doesn't receive enough oxygen. Another possible benefit of blood transfusion is that it may help people get out of bed more quickly after surgery. This is an important aspect of their recovery. However, blood transfusions can have side effects such as heart failure or increased infections after surgery, and these can delay people's recovery. Giving unnecessary blood transfusion might be harmful and expensive. Finally, transfused blood is a scarce resource that needs to be used carefully.

Although some research has been done in this area, doctors are still unsure of when to prescribe blood transfusions to these people. We are not sure about how low the blood count can safely be before a blood transfusion is ordered. Current guidelines recommend prescribing at a lower haemoglobin count, but there is research which suggests that this level is too low in people undergoing surgery for a fractured hip, particularly if the patient has a history of heart disease. In these people, transfusion at a higher level may be better to prevent heart attacks and similar complications.

PLANNED RESEARCH

We plan to undertake a study comparing blood transfusion at two different levels of anaemia to see which is best for people. Patients with a broken hip will be assessed to see if they are able to take part in this study. If they become anaemic in the period between admission and 7 days after their surgery, they will be allocated to receive a blood transfusion at one of two different blood count levels: a lower or "restrictive level" in line with current guidelines, or a higher "liberal" level. We will then measure the number of post-operative heart attacks and other complications, length of stay in hospital, death rate and quality of life. The results of this study will guide doctors looking after these people as to when blood transfusion will be beneficial.

TEAM FOR DELIVERY

The proposed trial has been developed by an experienced multi-professional team with patient involvement throughout. Patient groups have been involved in the design of this study and in reviewing the information we plan to give to people. We will involve the Perioperative Medicine Clinical Trials Network, a group set up to deliver this type of research.

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LIST OF ABBREVIATIONS

4AT	4 “A”s Test (For delirium)
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AKI	Acute Kidney Injury
AMTS	Abbreviated Mental Test Score
AoA	Association of Anaesthetists
ASA-PS	American Association of Anaesthesiologists – Physical Status
CDC	Centre for Disease Control
CFS	Clinical Frailty Score
CHI	Community Health Index
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CVD	Cardiovascular Disease
DMEC	Data Monitoring and Ethic Committee
EQ-5D-5L	EuroQoL-5 Dimension-5 Levels
GCP	Good Clinical Practice
Hb	Haemoglobin
HE	Health Economics
HIS	Health Improvement Scotland
HRQoL	Health Related Quality of Life

ICH	International Conference on Harmonisation
ISF	Investigator Site File
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major Adverse Cardiac Events
MDT	Multidisciplinary Team
MI	Myocardial Infarction
MINS	Myocardial Injury after Non-cardiac Surgery
NHFD	National Hip Fracture Database
NI	Northern Ireland
NICE	National Institute for Health and Care Excellence
PE	Process Evaluation
PI	Principal Investigator
QA	Quality Assurance
Tn	Troponin
TMF	Trial Master File
RBC	Red Blood Cells
REC	Research Ethics Committee
SDM	Surrogate Decision Maker
SHFA	Scottish Hip Fracture Audit
SIGN	Scottish Intercollegiate Guideline Network
SOP	Standard Operating Procedure
TACO	Transfusion-associated circulatory overload
U&Es	Urea and electrolytes

INTRODUCTION

1.1 BACKGROUND

1.1.1 Hip fracture

Hip fracture is a huge challenge facing populations and healthcare systems. Globally, hip fracture affects 1.3 million people annually and by 2050 this figure is estimated to rise to 6 million.(1) In the UK, over 70,000 are affected annually(2) and the figure could exceed 100,000 within the next two years.(3) The global cost of hip fracture is estimated at 1.75 million disability adjusted life years lost: 1.4% of the total healthcare burden in developed economies.(4) Hip fracture care is a major acute activity in all UK NHS Trusts. Almost all those affected will undergo surgery and around 3600 acute hospital beds are occupied every day by people with hip fracture (about 1 in 45 of NHS hospital beds). The estimated annual cost is over £1 billion.(5) Since 2007 the National Hip Fracture Database (NHFD) has collected data on activity, case mix adjusted outcomes and key performance indicators to drive quality improvement in this group and it represents a key priority for progressive care improvement across the NHS. In Scotland the Scottish Hip Fracture Audit (SHFA) undertakes a similar role.

Hip fracture has a significant impact on health. People with this condition are typically elderly, with high rates of comorbidity including cardiovascular disease (CVD), renal and cognitive dysfunction. The mean length of hospital stay in the UK (excluding Scotland) is 15 days; importantly, 19% of those who survive do not return to their original residence with a high rate of increased dependency. The rate of concurrent multi-morbidity is high, especially for chronic cardiovascular disease (CVD) which is consistently estimated at over 60% in this population, for example in pilot data,(6) metanalysis (7) and in large prospective trials.(8) According to the NHFD (which collected data on over 67 000 people in 2019) 30-day mortality was 6.5% in the UK in 2019; this figure rises to 30% at one year.

Rates of postoperative complications are also high and these include major adverse cardiac events (MACE), renal and neurological dysfunction.(2, 6, 9) In particular, cardiac and infectious complications have been demonstrated to be leading causes of acute hospital mortality in these people.(10) The rate of myocardial infarction (MI) is estimated at approximately 4%. The combined rate of all cardiac complications is higher, and is estimated at between 6-10% from prospective studies, metanalysis, and in pilot data from our group that informed this trial.(6, 8, 11, 12) (NCT03407573). Importantly, these complications occur more frequently in anaemic people.(13) Postoperative infections are also common, occurring in 10-20% of people based on the same data sources.

The 4th Universal Definition of Myocardial Infarction (2019) recognises that perioperative MI is a major complication after non-cardiac surgery, and it is associated with a poor prognosis. Many patients who have a perioperative MI do not experience cardiac symptoms due to anaesthesia and analgesia. Myocardial injury after non-cardiac surgery (MINS) is cardiac injury after surgery, evidenced by elevated troponin in the absence of typical symptoms of myocardial infarction. It is a common and clinically relevant occurrence in patients undergoing high risk surgery (such as for hip fracture). MINS is independently and strongly associated with both short-term and long-term mortality, in the absence of clinical symptoms, ECG or other evidence of myocardial

infarction. Consequently, surveillance of myocardial injury after noncardiac surgery has been recommended in patients at high risk for perioperative cardiovascular complications.(14) Population characteristics in hip fracture may also mask symptoms: dementia, acute or chronic confusion, poor reporting, busy wards and distracting injuries, making this outcome highly relevant.

In 2022 the American Heart Association published a scientific statement on MINS including definition, epidemiology, pathophysiology, prediction, surveillance, prevention, prognosis, and management. (15) MINS is defined as follows: elevated postoperative troponin above the upper reference limit (URL) with a rise/fall pattern indicative of acute myocardial injury; occurs in the first 30 days (and typically within 72 h) after surgery; attributable to a presumed ischemic mechanism; clinical symptoms masked by sedation or analgesia in the perioperative setting, ischemic features (e.g. ECG, echocardiographic changes) not required..

Large epidemiological studies suggest MINS occurs in 20% of patients who have high-risk inpatient surgery, and most are asymptomatic.(16) In the orthogeriatric population this is approximately 40% (17) and data from our pilot and observational studies suggest that in anaemic subgroups this is even higher at 60%. (6, 11) Anaemia is a strong risk factor for myocardial ischaemia based on normal coronary physiology and pathophysiology in patients with coronary disease. A recent analysis of 6141 adults who had postoperative troponin measurements as part of the ENIGMA-2, POISE-2, VISION and BALANCED trials found that postoperative haemoglobin anaemia was associated with increased MINS. Whether this association is modifiable by prevention or treatment of anaemia remains undetermined.(18)

1.1.2 Perioperative anaemia and transfusion practice

Anaemia is common in people experiencing hip fracture and is multifactorial, arising from either chronic disease or blood loss at the time of injury or surgery.(13, 19, 20) Data from our pilot work suggests that people who experience a fall in their Hb to 90 $g.L^{-1}$ or less, which is generally considered moderate to severe anaemia, usually do so within the first three days of surgery. Available evidence generally supports restrictive transfusion strategies in stable hospitalised adults but uncertainty exists for important patient subgroups, notably those with coexisting CVD. (21) These people were excluded or under-represented from many of the large trials in this area. Importantly, a systematic review (SR) and meta-analysis by members of our group suggested that people with chronic CVD experience higher rates of MI and a trend towards higher mortality when managed with restrictive transfusion strategies.(12) As described above, the hip fracture population is typically elderly, commonly multimorbid, and frail with a high rate of coexisting CVD and anaemia. Non transfusion treatments for anaemia during the acute phase of illness, such as intravenous iron, are not supported by high quality evidence at present.(22) Blood transfusions are prescribed frequently, and this population is one of the largest single groups receiving red blood cell (RBC) transfusions annually. As such this is a key high-volume population in whom improving the evidence base for optimum transfusion practice has potential for health and economic benefit.

At December 2020, six relevant systematic reviews (SR) since 2015 considering the issue of transfusion have been published (7, 9, 12, 22-24) these relate directly to people with fractured neck of femur (7, 9, 22) or undergoing surgery (12, 23) or the elderly.(24) The overall quality of the evidence is low, and these studies report inconsistent effects of restrictive transfusion

strategies. Moreover, there are a range of transfusion triggers used by each study and no standard definition of a restrictive or liberal strategy.

1.1.3 Current Transfusion Practice

Chronic anaemia is common in people presenting with hip fracture, which combined with bleeding results in high perioperative RBC transfusion rates. Around 30% of all people receive an RBC transfusion.(20, 25) People commonly receive red cell transfusions to increase haemoglobin concentration with the belief that this may increase oxygen delivery to the tissues, particularly to the myocardium, and improve clinical outcomes. Clinicians believe this may prevent cardiac complications, improve mobilisation, and reduce hospital stay.(26, 27) However, blood components are biological agents, with uncertain risks including Transfusion-associated circulatory overload (TACO) immunosuppression and immunomodulatory effects which may increase infectious complications.

The results of a recent survey of over 200 UK clinicians demonstrated a range of transfusion thresholds in clinical use before, during and after surgery for hip fracture, depending on the presence of cardiovascular disease. 50% of clinicians indicated that they would transfuse at a higher trigger than 70 $g.L^{-1}$ even if there was no coexisting CVD, and only 25% would use this threshold in the presence of stable or recent CVD. The main concerns around transfusion were anaphylaxis, lung injury and transfusion related circulatory overload (TACO).(28) The risk of TACO, which is often underreported, is greater in elderly people with CVD as a result of low body mass and potentially impaired cardiac and/or renal function.

Current guidelines from professional bodies also vary in their recommendations in relation to transfusion practice for people with hip fracture. The National Institute for Health and Care Excellence (NICE) recommends considering 'a threshold of 70 g L^{-1} and a haemoglobin concentration target of 70–90 g L^{-1} after transfusion' and made a research recommendation for more research in people with chronic cardiovascular disease. The American Association of Blood Banks guideline (AABB) recommends for people undergoing orthopaedic surgery and those with pre-existing cardiovascular disease a restrictive RBC transfusion threshold of 80 g L^{-1}.
The Association of Anaesthetists (AoA) guideline for the use of blood components recommends a default Hb transfusion threshold of 70 g L^{-1} but notes uncertainty among people with ischaemic heart disease. Of note the AAGBI guideline for hip fracture management noted that the 'risks of anaemia-related organ ischaemia (heart, brain, kidneys) need to be balanced against the immunosuppressive effects of blood transfusion in older people with hip fracture on a case-by-case basis'. The working party stated 'that peri-operative Hb in frailer patients should be kept above approximately 90 g $L^{-1,}$ or approximately 100 g L^{-1} for patients with a history of ischaemic heart disease or who fail to remobilise on the first postoperative day due to fatigue or dizziness. These contradictory recommendations illustrate current uncertainties and the need for high quality evidence. (29, 30)

1.1.4 Pilot Study Results

Our group have undertaken a single centre pilot RCT in 200 people exploring the effect of restrictive versus liberal transfusion practice on cardiac injury following surgery for hip fracture (Clinical trials NCT03407573).(11)

This demonstrated the following key findings in the UK hip fracture population:

- the mortality at 30 days in this group is 6-7%
- the rate of co-existing cardiovascular disease is over 60%.
- the transfusion rate in this group is approximately 30%.
- the incidence of *clinically diagnosed* cardiac complications following hip fracture surgery in anaemic people is 14%.
- the incidence of MINS (perioperative elevated troponin) in anaemic people following hip fracture surgery is over 60%.

Our pilot study concluded that a trial of restrictive versus liberal transfusion practice was feasible but that transfusion before reaching the trigger of 70 $g.L^{-1}$ in the restrictive group was the leading cause of protocol deviation. Overall protocol compliance was 64% in the restrictive group and 81% in the liberal group suggesting that many clinicians would prefer to transfuse at a higher Hb target than 70 $g\ L^{-1,}$ consistent with the variation in national and international guidance.

1.2 RATIONALE FOR STUDY

1.2.1 Research Hypothesis

We hypothesise that a more liberal postoperative transfusion strategy will reduce death and major cardiovascular complications in people with hip fracture and anaemia, compared with currently recommended more restrictive transfusion strategies. We hypothesise that a more liberal blood transfusion practice will be cost-effective in this population.

1.2.2 Benefits of the study

The evidence base for best practice in this group is uncertain, especially in the presence of cardiovascular disease, and guidelines are inconsistent and not followed reliably, leading to substantial variation in clinical practice. Better evidence to guide the clinical and cost-effectiveness of RBC transfusion in this group will reduce variation, improve clinical outcomes, and generate economic and efficiency benefits for the NHS in one of its largest emergency populations. Evidence-based personalised anaemia management could substantially improve people's health, reduce healthcare costs, and relieve unscheduled care bed pressures. The results of the study may contribute to guidance for clinicians via NICE and HIS/SIGN for management of hip fracture, and dissemination of results to improve clinical care via clinical networks. The findings of this research may also inform blood management of other high risk groups undergoing surgery.

1.2.3 Study treatment under investigation: liberal vs restrictive blood transfusion strategy

The intervention being investigated is postoperative blood transfusion using different haemoglobin triggers.

The blood product will be standard issue RBCs produced by transfusion services and issued according to routine clinical practice. The treatment arms of this study will be "liberal" and "restrictive". The "liberal" group will be transfused at a threshold of Hb 90 $g.L^{-1}$ or less (post-transfusion target Hb 90-110 $g.L^{-1}$) from randomisation until acute hospital discharge or 30 days post-randomisation, whichever is sooner. This is more liberal than current guidance but consistent with practice and beliefs of many clinicians in this population for the reasons which have been outlined earlier. This practice is like that recommended by the AoA working group for hip fracture and included in the AAGBI hip fracture guideline.

The "restrictive" transfusion group will be transfused at a threshold of 75 $g.L^{-1}$ or less (post-transfusion target Hb of 75-90 $g.L^{-1}$) from randomisation until acute hospital discharge or 30 days, whichever is sooner. As noted above, NICE guidance suggests a transfusion trigger of 70 $g.L^{-1}$ or less and that Hb should be maintained in the 70-90 $g.L^{-1}$ range, however other available guidance suggests a higher trigger of 80 $g.L^{-1}$. In our pilot study some clinicians were unwilling to wait until Hb fell to below 70 $g.L^{-1}$ before prescribing a blood transfusion. Therefore, to best represent acceptable current practice, and improve compliance in this arm, a trigger of 75 $g.L^{-1}$ or less was chosen to maintain optimal compliance while ensuring that participants' Hb remained within the desired range. This practice is therefore like that recommended by most generic transfusion-specific guidelines.

In both groups single unit RBC transfusions will be given followed by Hb reassessment, consistent with best practice guidelines. (29, 31)

1.2.4 Desirable study outcome

In people with hip fracture, we estimate 30-day all-cause mortality will be 7%, rates of MACE will be 10%, and rate of new MINS will be 20%. These rates may be higher in the anaemic populations being included in this study. We consider an absolute risk reduction (ARR) of 5% in the combined primary outcome of MACE, new MINS and death to be a realistic meaningful effect size that would change clinical practice (33% Relative RR). This would represent a number needed to treat (NNT) of 20 for every patient receiving liberal transfusion to avoid a death or MACE or new MINS outcome compared to the restrictive group.

STUDY OBJECTIVES

1.3 OBJECTIVES

1.3.1 Primary Objective

To determine if a liberal postoperative transfusion strategy (transfused at a threshold of Hb 90 $g.L^{-1}$ or less) will reduce death and major cardiovascular complications, compared with practice recommended in many transfusion guidelines (restrictive transfusion strategy), in people with hip fracture and anaemia.

1.3.2 Secondary Objectives

Our secondary objective is to determine whether a liberal postoperative transfusion strategy will improve quality of life at 120 days and reduce costs in people with hip fracture and anaemia, compared with usual care.

At 30 days we will assess the impact of a liberal postoperative transfusion strategy on: all-cause mortality; Myocardial Injury (defined as detectable troponin release above the Upper Reference Limit (URL)); individual MACE components; new MINS; other complications (including acute kidney injury [AKI], infection, delirium); proportion transfused; volume of blood transfused; discharge destination; hospital length of stay, HRQoL (EQ-5D-5L)

At 120 days we will assess the impact of a liberal postoperative transfusion strategy on: all-cause mortality; secondary care costs; unplanned hospital readmissions within 120 days; mobility (as defined by NHFD dataset); residential status (as defined by NHFD); HrQoL (EQ-5D-5L).

1.4 ENDPOINTS

1.4.1 Primary Endpoint

The primary outcome will be death OR major adverse cardiac events (MACE) OR new myocardial injury after non cardiac surgery (new MINS) within 30 days of randomisation.

MACE will be defined as any combination of the following:

- Myocardial Infarction: Diagnosed using the 4th Universal Definitions for MI(14)
- New Arrhythmia: ECG confirmed arrhythmia resulting in a fall in mean arterial pressure of >20% *and requiring pharmacological or cardioversion treatment*.
- Cardiac or respiratory arrest: Resuscitation Council UK definitions
- Cardiogenic pulmonary oedema.

New MINS will be defined as : new elevated postoperative troponin above the upper reference limit (URL) with a rise/fall pattern indicative of acute myocardial injury occurring in the first 30 days (and typically within 72 h) after surgery; attributable to a presumed ischemic mechanism,

clinical symptoms masked by sedation or analgesia in the perioperative setting, ischemic features (e.g. ECG, echocardiographic changes) not required.

To maximize validity and consistency, all participants will have troponin measured at randomisation (baseline), and then twice more in days 1 to 5, ideally on the 1st and 3rd calendar days after randomisation with all samples being at least 24h apart from each other, and 12-lead ECGs will be performed at baseline and repeated once in days 2 – 5. The primary outcome will be determined by an expert adjudication team blinded from group allocation.

1.4.2 Secondary Endpoints

Secondary outcomes at 30 days are as follows:

1. All-cause mortality
2. New Myocardial Injury post-randomisation (New MINS)
3. Individual MACE components (including type of arrhythmia)
4. Complications (including AKI, infection, delirium)
5. Proportion of participants transfused; volume of blood transfused per patient
6. Discharge destination (home, other hospital, nursing home, other)
7. Acute hospital length of stay
8. ED-5D-5L

Additional secondary outcomes at 120 days are as follows:

1. All cause mortality
2. Secondary care costs
3. Unplanned hospital readmissions
4. Mobility (as defined by NHFD or SHFA dataset
5. Residential status (as defined by NHFD or SHFA dataset)
6. EQ-5D-5L
7. Health services resource use

Clinical outcomes will be measured until acute hospital discharge or 30 days post randomisation whichever is soonest. Death, readmission, mobility, residential status, quality of life and resource use will be measured at 120 days post-randomisation.

2 STUDY DESIGN

2.1 STUDY DESIGN

RESULT-Hip is a multicentre, parallel-group randomised controlled clinical and cost effectiveness trial with internal pilot of two transfusion strategies in people with hip fracture. Participants will be allocated to each treatment arm using a web-based allocation system at random in a 1:1 ratio.

2.1.1 Internal pilot

In a 6-month internal pilot we will aim to open at least 10 sites and randomise at least 150 participants. We will collect data on screening, patient/clinician refusal, and undertake telephone interviews with sites to discuss recruitment and trial fidelity. We will also hold focus groups with patients and clinicians to examine barriers to recruitment and protocol compliance and ensure best practice.

2.1.2 Process Evaluation

We will include a process evaluation (PE) of the internal pilot study, consistent with MRC guidance,(32) to explore the processes involved in delivering the intervention and any facilitators or barriers to recruitment. Our objectives are to establish the extent to which the intervention is implemented as intended during the internal pilot across different sites; to ascertain how feasible and acceptable the intervention is to clinical staff across different sites; to identify any facilitators and barriers to recruitment.

The methods used to conduct the PE of the internal pilot will be:

- During site initiation: At site initiation visits we will identify key research staff, collect baseline data on context and establish acceptability of the study protocol. These data will inform feasibility and any changes required to maximise recruitment and fidelity of the trial protocol for the main study as well as developing relationships with sites involved in the internal pilot.
- During the internal pilot: All sites in the internal pilot will be invited to participate in individual telephone interviews. The interviews will be undertaken with a member(s) of the research team which may include the PI, an investigator or a research nurse/ co-ordinator and a clinician from each site. Purposive sampling will be used to recruit a range of participants according to grade, profession and role in the research or clinical teams.

We will use a framework approach to analyse the qualitative data as this offers a systematic and flexible approach. Themes identified *a priori* alongside those generated through the iterative process of collecting and analysing data will lead to the development of the final analytical framework. Trustworthiness criteria will be considered at each stage to ensure the quality of the process evaluation. The researcher will keep an audit trail of decisions around sampling and analysis to ensure confirmability and dependability, thick description of the process will support transferability, and credibility will be achieved through informal member checking with participants during interview and independent coding of a sample of interview data.

2.1.3 Trial Progression

Trial progression beyond the internal pilot phase will be based on TSC, DMC and HTA review of the PE and the following metrics.

"Red/Amber/Green" trial progression criteria:

- sites open/recruiting (<5 red; 5-10 amber; >10 green).
- Participants recruited (<75 red; 75-130 amber; >130 green).
- protocol adherence: adherence defined as transfusion only after checking Hb and transfusion consistent with predefined haemoglobin trigger. Based on deviations/violations we will use the following system: <70% red; 70-90% amber; >90% green).
- Recruitment rate/site/month open (<2.2 red; 2.2-3.7 amber; >3.7 green)

2.2 CENTRES

Most acute hospital trusts manage people with hip fracture as part of their usual emergency workload: this makes many UK hospitals available as potential recruiting sites.
We intend to recruit 25 - 30 sites to participate in this trial. The average trauma unit treats 400 people with hip fracture per year, but some high-volume centres treat over 800.

It is planned that 10 pilot sites will open at a rate of 2 sites per month and will aim to recruit, on average, 4.3 participants per site per month open. Following the 6-month internal pilot, it is anticipated sites will continue to open at a rate of 1-2 sites per month until the full complement of 25 - 30 sites is achieved Recruitment rates during this period areestimated at 1.3-1.6 patients per site per month open. In total, there will be 51 months of recruitment, cumulating to around 900 centre-months of available recruitment time.

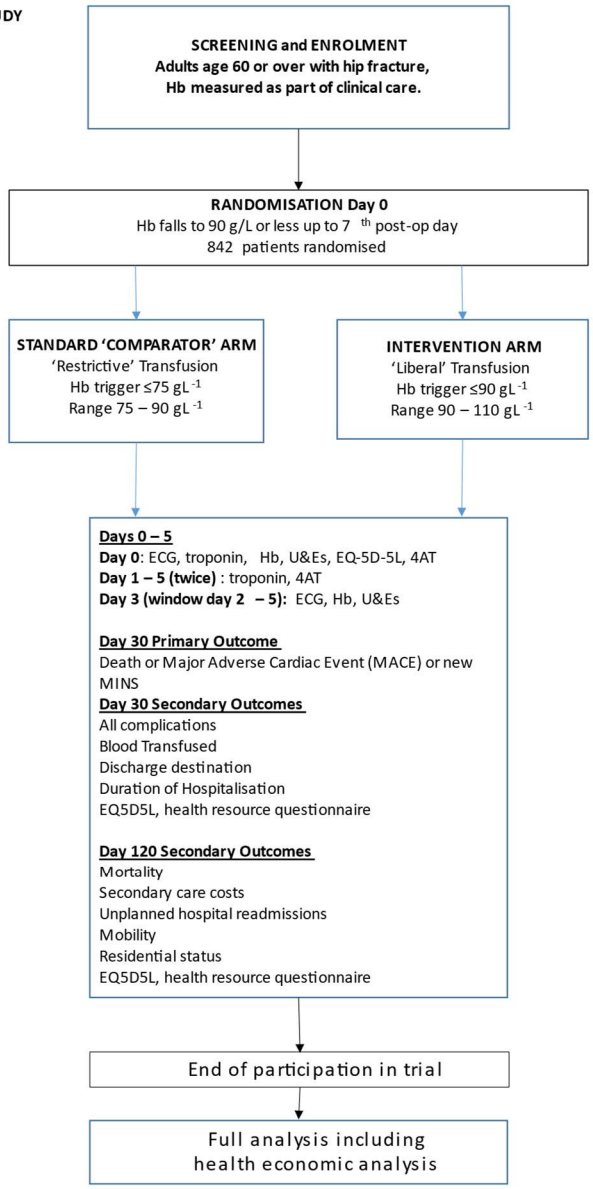
2.3 DURATION OF PARTICIPANT INVOLVEMENT

We will screen people with hip fracture who meet the age inclusion criteria. This can take place from the time the patient enters the hospital and up to and including 7 days post –surgery. Once potential participants have been identified they will be followed daily to check the haemoglobin level measured on their blood results. If a haemoglobin measurement triggers inclusion in the study, that is, if the Hb falls to 90 $g.L^{-1}$ or less, then the patient will be randomised. Randomisation should take place as soon as possible after the triggering haemoglobin measurement and no later than post-operative day 8. This can occur pre-operatively or postoperatively whenever on the patient journey that the Hb value first falls to 90 $g.L^{-1}$ or less.

Participants who are randomised in the study follow one of two arms: restrictive or liberal blood transfusion. Both arms have the same measurements, data collection and follow up. The participants will be in the study for up to 120 days from entry. Participants will be sent a summary of the study results at the end of the trial by the University of Edinburgh if permission is given to do so. Thereafter there will be no further participant-researcher interactions.

2.4 PATIENT FLOW THROUGH STUDY

Figure 1 : STUDY FLOWCHART



3 STUDY POPULATION

3.1 NUMBER OF PARTICIPANTS

The sample size calculated for this study is 842 participants, with 421 in each arm of the study. This allows for a 10% dropout rate and is based on pilot data and expert opinion. We expect an incidence rate for the primary outcome of 15% at 30 days. An absolute risk reduction (ARR) of 5% in the primary outcome is a realistic and meaningful effect size that would change practice (33% Relative RR; Number Needed to Treat, 20).

3.2 RECRUITMENT PERIOD

The total project duration is 69 months.
In month 1-12 we will undertake approvals, set-up, and 10-site internal pilot.
In months 13 – 45 we will set-up the remaining 20 sites; months 25 – 57 will be the main recruitment phase.
In months 58 – 69 we will complete follow-up, analysis, report writing.

3.3 SITE INVOLVEMENT

After an initial 10 site internal pilot 20 further sites will be opened. This should fulfil the target recruitment over 24 months, at a rate of 4 participants/month.

If recruitment falls behind target, then further sites may be invited to join the study: most UK hospitals will be managing people with hip fracture regularly as part of their predictable emergency workload.

3.4 INCLUSION AND RANDOMISATION CRITERIA

Inclusion Criteria

- Adults aged 60 years or over
- Admitted to acute hospital unit for operative management of hip fracture

Randomisation Criteria

- Presence of anaemia (Haemoglobin equal to or less than 90 $g.L^{-1}$) at any time from admission until the seven days following surgery

3.5 EXCLUSION CRITERIA

- Objection to RBC Transfusion
- Unable to obtain consent (from patient or in accordance with appropriate mental capacity legislation for the site)
- Patient for non-operative management or not expected to survive 48 hours

- Patient with a new or suspected acute coronary syndrome meeting 4th Universal Definition(35) during current admission.
- Rapid or uncontrolled blood loss resulting in haemodynamic instability
- Chronic anaemias requiring repeated transfusion (e.g. Myelodysplasia or bone marrow failure syndromes)

3.6 CO-ENROLMENT

Co-enrolment will be permitted if in accordance with ACCORD Co-enrolment Policy (POL008 Co-enrolment Policy) and agreement of relevant CIs.

4 PARTICIPANT SELECTION AND ENROLMENT

4.1 IDENTIFYING PARTICIPANTS AND OVERVIEW OF CONSENT PROCEDURES

Potential participants will be identified by the clinical teams or the local research team (if part of the clinical care team), either in the emergency department or after admission to a hospital ward with a fractured hip. Identification could be through a combination of ward lists, theatre operating lists, trauma MDT meetings, or other sources. Clinical teams and members of the local research team (where they are part of the clinical team) may use information from hospital records to assess eligibility against inclusion and exclusion criteria. Where the clinical team is not part of the research team they will be asked to share information about potentially eligible participants with the research team.

Screening will occur daily from admission until 7 days post-surgery. The potential participant will be approached in person by a member of the clinical team or a member of the research team (where they are a member of the clinical team) to discuss whether they are interested in taking part in the study. Consent will be taken from eligible patients at any point during this period, based on all inclusion/exclusion criteria with the exception of the Hb trigger value (considered “consent in principle” or “pre-consent”), but will only be randomised if their Hb falls to ≤90g.L^{-1}

Where a participant is assessed as lacking capacity (by an appropriately trained member of the research team consulting with the patient's clinical care team where appropriate) the participant's nearest relative/welfare attorney/guardian/consultee will be consulted for advice about what the participant’s wishes and feelings would be if they were able to consent for themselves. This is permissible under the provisions of the Adults with Incapacity Act (Scotland) 2000, Mental Capacity Act (England and Wales) and Mental Capacity Act (Northern Ireland) 2016.

A more detailed description of arrangements by UK country is given in section 4.2

4.2 CONSENTING PARTICIPANTS

4.2.1 Screening

All people admitted with hip fracture will be screened daily for eligibility. A screening log will be maintained at each site which will include data on the numbers of people meeting inclusion criteria for the trial but not entered into the trial along with the reasons for non-enrolment. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement.

4.2.2 Consent

People who are potentially eligible and deemed capable of providing informed consent by the clinical and/or research team will be given a patient information leaflet to read which will fully explain the study with its risks and benefits. A summary sheet and an animated study video (if available) may be provided first to provide a brief outline of the study and allow potential participants to decide whether they wish to proceed before the full PIS is provided. This will then be discussed with them, and consent will be sought by an appropriately trained member of the research team. In patients with visual impairments, this information will be given verbally by a member of the research team.

If the participant agrees to enrol in the study, they will be asked to sign the consent form, which will then be countersigned by a member of the research team. Written consent will be sought from the participant wherever possible, but if a participant is unable to write, verbal consent can be taken. Verbal consent must be witnessed by an independent person that is not part of the research team for the study.

The participant will be provided with a copy of the consent form, a copy of the form will be filed in the participant's medical notes and a copy filed in the ISF. The informed consent process must be documented in the participant's medical records.

Wherever possible, potential participants will be approached as early as possible following admission to provide consent to participate in the trial. This is referred to as "pre-consent" and participants will only be randomised if their haemoglobin concentration decreases to 90g L^{-1} or less during the period from hospital admission to the seventh day following surgery. This approach will maximise the time available for participants and their nearest relative/guardian/welfare attorney/consultee to decide whether they wish to take part in the trial, prior to developing anaemia and also minimise delays in transfusion once patients become anaemic.

4.2.3 Consent for people without capacity

Some people may be unable to give informed consent because of pain, delirium, or cognitive impairment. This may be temporary, but in the case of people with dementia, loss of capacity may be permanent. Elderly adults with hip fracture are a patient group with a high rate of incapacity both from pre-existing cognitive impairment and/or because of the acute injury. Hip

fracture and the associated pain and requirement for analgesia also contribute to a high prevalence of delirium, which can also impair mental capacity. Identification of the contribution of pre-existing and acute incapacity is extremely challenging and may not be possible in a high proportion of cases. However, it is vital to include people with both pre-existing and acute incapacity, or a mixed picture, in the trial to ensure its relevance and generalisability. It is also biologically plausible that the intervention could modify acute incapacity due to delirium, which is an important secondary outcome.

Eligible participants who are assessed as lacking capacity to consent will be enrolled in the study in accordance with the legal requirements of that part of the devolved nations where recruitment is taking place. Consequently, different processes will apply in different UK devolved administrations, and a flow-chart describing this is provided in APPENDIX E.

4.2.3.1 Making decisions for people without capacity in England, Wales, and Northern Ireland

The Mental Capacity Act (Northern Ireland) 2016 is closely aligned with the Mental Capacity Act 2005, which applies in England and Wales. A scheme of mutual recognition of NHS/HSC research ethics committee (REC) review for research involving adults lacking capacity to consent has been agreed between these three nations, therefore for the purposes of the trial, processes used in England and Wales will be used in Northern Ireland.

If there is a person willing and able to take on the responsibilities of Personal Consultee/, a trained member of the research team will describe the trial to the individual and provide them with a Personal Consultee Information Sheet. A summary sheet and an animated video (if available) may be provided first to provide a brief outline of the study and allow the Personal Consultee of potential participants to decide whether they wish to proceed before the full information sheet is provided. It is preferable to seek advice from personal consultees in person but in circumstances where this is not possible, advice can be sought by telephone and a declaration completed in the presence of an independent witness who is not part of the study research team. If a declaration is completed over the telephone the personal consultee should be asked to sign the declaration at the earliest opportunity. Recruitment to this study is time critical, therefore if a Personal Consultee is not available to provide advice within an appropriate timeframe (all transfusions should ideally be given within 24 hours, or within 48 hours at the latest) then a suitable independent individual not directly involved in the trial and prepared to act as a Nominated Consultee will be consulted and will be informed about the trial by a member of the research team and given a copy of the Nominated Consultee Information Sheet. If the independent Nominated Consultee agrees, the member of the research team will recruit the patient into the trial. If a patient is randomised into the study via a Nominated Consultee, the Personal Consultee will be informed at the earliest opportunity and their opinion sought about whether the participant would want to continue to take part in the study.

The process will be documented in the patients' clinical notes.

4.2.3.2 Consent for patients without capacity in Scotland

Consent will be obtained in Scotland according to the Adults with Incapacity (Scotland) Act 2000). If there is a Welfare Attorney/Guardian or Nearest Relative an authorised staff member/researcher will describe the trial to the individual in person if possible, or alternatively by telephone or approved video consultation technology if attendance is not possible in a timely manner. The Welfare Attorney/Guardian or Nearest Relative will be provided with a Welfare Attorney/Guardian/Nearest Relative Information Sheet or the trial will be described by telephone/video consultation. A summary sheet and an animated video (if available) may be provided first to provide a brief outline of the study and allow the Welfare Attorney/Guardian or Nearest Relative of potential participants to decide whether they wish to proceed and before the full information sheet is provided.

If the Welfare Attorney/ Guardian/Nearest Relative agrees, then they will provide consent for inclusion. 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. Witnesses to consent taken over the telephone/approved video consultation technology must be independent of the study i.e. not part of the study research team.

In cases where no Welfare Attorney/Guardian/Nearest Relative is available it will not be legally possible to enrol a patient in Scotland.

4.2.3.3 Procedure if participants regain capacity

Once the participant has recovered from the condition causing incapacity, they will be approached by a member of the research team to obtain permission to continue in the study. The consent to continue process will include assessment and documentation of capacity; providing the PIL and Consent Form for Participant with Recovered Capacity; allowing sufficient time for the participant to understand the material and ask questions; and obtaining written informed consent. Participants with visual impairments will be given the information verbally by a member of the research team. If the participant agrees to continue in the study, they will be asked to sign the consent form, which will then be countersigned by a member of the research team. Written consent will be sought from the participant wherever possible, but if a participant is unable to write, witnessed verbal consent can be taken. Witnesses to verbal consent must be independent i.e. Not part of the study research team. The participant will be provided with a copy of the consent form, a copy of the form will be filed in the participant's medical notes and a copy filed in the ISF. The informed consent to continue process must be documented in the participant's medical records.

If the participant is discharged from hospital before regaining capacity, the research team will contact the participant's representative at the 30 and 120 day follow up timepoints to ascertain if capacity has been regained. If it has, the research team will discuss the study with the participant and seek consent from them to continue in the study. If the participant wishes to continue in the study, the research team will post the Recovered Capacity consent form to them, with a stamped addressed envelope for its return.

If the participant declines on-going participation in the study the procedures for withdrawal (below) will be followed. In the rare event that the patient does not regain capacity or staff have

been unable to obtain consent to continue, then : In Scotland, the consent from the Welfare Attorney/Guardian or Nearest Relative will continue; In England, Wales and Northern Ireland the advice from the Personal Consultee or Nominated Consultee will continue.

4.2.4 Withdrawal of Study Participants

Participants are free to withdraw from the study **at any point** or a participant can be withdrawn by the Investigator. In Scotland participants can be withdrawn by the Welfare Attorney/Guardian or Nearest Relative who gave consent for the participant to enter the study. In England, Wales and Northern Ireland participants can be withdrawn by the Personal or Nominated Consultee whose advice was sought and who completed a declaration that in their opinion the participant would have no objection to taking part in the study. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible.

The participant will have the option of withdrawal from:

1. Withdrawal from intervention only – permission given to contact participant for follow up questionnaires and to collect information from routine health records for the primary & some secondary outcomes

2. Withdrawal from intervention and any on-going aspects of the trial that require participant contact or completion of questionnaires but permission given to collect information from routine health records for the primary & some secondary outcomes

3. Withdrawal from all aspects of the trial but continued use of data up to that point

There are no early stopping rules or discontinuation criteria for this study.

4.3 RANDOMISATION

Participants should be randomised as soon as possible after the triggering haemoglobin measurement and no later than post-operative day 8.

Participants will be randomised by remote computer to ensure allocation concealment. Allocation will be in a 1:1 ratio with stratification by centre, age (<80 vs. ≥ 80 years) and pre-existing diagnosis of cardiovascular disease. Randomisation will be performed using a web-based randomisation system developed by the Edinburgh Clinical Trials Unit (ECTU).

Due to the nature of the intervention blinding of trial participants and local study teams will not be possible, however the primary outcome assessment will be adjudicated by a panel blinded to treatment allocation.

5 STUDY INTERVENTION

5.1 TRANSFUSION THRESHOLD

All eligible people admitted with hip fracture will be approached for this trial and enrolled if consent is given. As part of usual clinical care, all potential participants should have their Hb measured on admission, and usually an additional measurement if required preoperatively, and at least two measurements postoperatively. If an enrolled patient's haemoglobin is Hb 90 $g.L^{-1}$ OR LESS between admission and the first 7 days following surgery, based on routine clinical care measurements, they will be randomised to either restrictive (Hb 75 $g.L^{-1}$ OR LESS) or liberal (Hb 90 $g.L^{-1}$ OR LESS) transfusion strategy. After randomisation they will remain in this transfusion group for the duration of acute hospital stay (or 30 days post-randomisation whichever is shorter). The patient's clinical teams will be informed and made aware that they are in the study and are not blinded to randomisation group allocation.

5.2 STUDY INTERVENTION

5.2.1 Blood Transfusion

Once participants are randomised, the transfusion laboratory at the site will be informed of their treatment allocation by the research team. Where possible the blood transfusion laboratory will add a 'flag' to the participants record to ensure that the treatment arm is recorded, and that blood is released according to the patient's study group. Currently red blood cell transfusions are ordered and released using a combination of paper and electronic requests and this will need to be tailored according to the individual site's processes.

Intervention: liberal transfusion protocol
Participants randomised to the liberal arm will receive one unit of red blood cells as soon as possible after randomisation (ideally within 24 hours) to keep their haemoglobin within the range of 90-110 g. L^{-1}. Participants should receive any subsequent transfusions within 24 hours of an Hb of 90 $g.L^{-1}$ or less. Transfusions that do not occur or occur > 48 hours post-randomisation will be considered a protocol deviation as detailed in section 13.2.

Comparator: restrictive transfusion protocol
Participants randomised to the restrictive arm will not receive a blood transfusion until their haemoglobin falls to 75 $g.L^{-1}$ or less and the aim will be to keep their haemoglobin within the range 75-90 $g.L^{-1}$. Participants should receive a blood transfusion within 24 hours of an Hb of 75 $g.L^{-1}$ or less. Transfusions that do not occur or occur >48 hours after an Hb of 75 $g.L^{-1}$ or less will be considered a protocol deviation as detailed in section 13.2.

In all participants these targets apply for the duration of acute hospital admission or 30 days post-randomisation whichever is soonest. Single units of red blood cells will be given, and the haemoglobin rechecked before a further transfusion, unless the responsible clinician decides

that multiple red blood cell units are indicated. Situations may arise where a participant has a further haemoglobin measurement **after** the threshold Hb measurement , but **before** a transfusion is given, which alters the requirement to transfuse. In this case, clinicians should use the most recent Hb measurement to determine whether a transfusion is required, the aim being to follow the protocol as closely as possible to keep participants in their allocated Hb range of restricted or liberal.

Acceptable methods of checking haemoglobin include FBC, haemocue or arterial blood gas measurement, depending on local practice, however when point of care testing is used it is recommended that a full blood count is performed as soon as practicable.

For patients recruited prior to surgery clinicians should follow the protocol as closely as possible in the operating theatre, using point of care haemoglobin measurement.

In the case of life threatening or rapid uncontrolled bleeding e.g., major haemorrhage, or major blood loss in the operating theatre or elsewhere, there can be a temporary suspension of the study protocol and the clinical team may transfuse at physician discretion.

If there are other significant clinical safety concerns related to anaemia in any clinical setting (ward or operating theatre), participants can be transfused before the Hb reaches 75g/L but efforts should be made to maintain Hb within the allocated range.

Any transfusion in circumstances described above should be recorded as a protocol deviation as detailed in section 13.2.

5.2.2 Other study interventions

Participants pre-consented to take part in RESULT-Hip but not yet randomised

All participants enrolled in RESULT-Hip will have their haemoglobin and U&Es (urea and electrolytes) measured as per local practice. This must include a measurement preoperatively and on the first and second postoperative days at a minimum. Additional blood sampling will be at the discretion of the clinical team

Participants randomised to the study intervention (both arms)

All participants randomised to RESULT-Hip will have their haemoglobin and U&Es (urea and electrolytes) measured as per local practice. We would expect participating sites to measure Haemoglobin pre-operatively and, on the first, and second post-operative days as part of routine care.

Haemoglobin and U&Es will be measured at randomisation (baseline) and once more in days 2 – 5. Blood samples for troponin analysis (analysis to take place in Edinburgh, results not

available to clinical team) will be taken at randomisation (baseline) and then twice more in days 1 to 5, ideally on the 1st and 3rd calendar days after randomisation with all samples being at least 24h apart from each other. The baseline sample should be taken as soon as possible after randomisation (on the same day and ideally within 4 hours of randomisation). ECGs will be performed at baseline and repeated once in days 2 – 5.

If it is anticipated that the participant will be discharged before Day 3, these assessments should be carried out pre-discharge.

Haemoglobin will also be measured as soon as possible after every transfusion given as part of the study (ideally within 24 hours).

Additional blood sampling will be at the discretion of the clinical team unless Haemoglobin is not measured as part of routine care for 5 consecutive days. The protocols for blood sampling and measurement in each study site will be checked and clarified during site set-up.

4AT assessment will be carried out at randomisation, and then twice more in days 1 to 5, ideally on the 1st and 3rd calendar days after randomisation.

EQ-5D-5L will be measured at randomisation, or as soon as practicable after, and at days 30 +/- 7 days and at day 120 +/- 7 days.

Health services utilisation will be measured by questionnaire at 30 +/- 7 days and 120 +/- 7 days.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Assessment	Screening & Enrolment	Randomisation (baseline) Day 0	Day 1 - 5	Day 3 (range 2 - 5)	Day 30	Day 120
Assessment of eligibility criteria	X					
Written Informed Consent	X					
Demographic Data, Contact details, GP details, PMH, CFS, AMTS or AMT4		X				
Intraoperative data		X				
Blood sample- Haemoglobin	X	X		X		
Blood sample - U&E's		X		X		
ECG		X		X		
Blood sample - Troponin		X	XX*			
4AT		X	XX*			
Blood transfusions. Pre and post transfusion haemoglobins					X	
Hospital length of stay					X	
Readmission					X	X
Complications including MACE					X	
Mortality					X	X
EQ5D5L		X			X	X
Health services utilisation questionnaire					X	X

*Blood sampling for troponin analysis and 4AT to be performed twice in days 1 to 5, ideally on the 1st and 3rd calendar days after randomisation, with all blood samples being at least 24h apart from each other.

6.2 LONG TERM FOLLOW UP ASSESSMENTS

Participants will be prospectively followed up in person or by accessing paper and electronic records until acute hospital discharge or 30 days post-randomisation, by the research team. The research team will access hospital records for up to 120 days to capture data regarding cardiac events and other complications, hospital readmissions and mortality. Where a participant has died the cause of death will be recorded from the death certificate or medical record.

Survival status will be confirmed by the participating sites, by checking hospital records, prior to attempting to contact the participant in hospital or by telephone at home at 30 and 120 days to administer EQ-5D-5L and health economic follow up questionnaires. In participants who have

not regained capacity before discharge from hospital, the research team will attempt to gain consent as described in section 4.2.2.3. Where capacity has been regained the research team will contact the participant to administer the questionnaires. Where capacity has not been regained, the research team will contact the participant's representative to ask them to complete the questionnaires on behalf of the participant. If the research team is unable to contact the participant, or their representative, by telephone, the questionnaires will be posted.

6.3 STORAGE AND ANALYSIS OF SAMPLES

Blood samples for full blood count and urea and electrolytes will be collected at randomisation, then on post randomisation day 3 (window day 2 – 5) and thereafter at the discretion of the clinical team. These will be analysed locally in routine NHS laboratories as part of routine care, and the results recorded in the CRF by the local study team.

The serum troponin measurement will be used to define the primary endpoints and secondary endpoints relating to cardiac complications. Blood will be taken for serum troponin measurement at randomisation, then twice more in days 1 to 5, ideally on the 1st and 3rd calendar days after randomisation with all samples being at least 24h apart from each other. Where possible these will be timed with routine blood sampling as part of normal clinical care. These samples will be drawn by venepuncture (or by arterial or central venous catheter if available) into serum gel. Blood should be allowed to clot for a minimum of 30 minutes then spun as soon as possible, ideally within 2 hours of sample collection. If serum gel is not available at a site, Lithium-Heparin tubes can be used, and separate instructions will be issued for sample processing.

Samples should be labelled and stored at -70C or lower until they are transported to Edinburgh for analysis. Study samples will be shipped from site and stored centrally. Frequency of shipments will be agreed on a per-site basis. Samples will be sent on dry ice to the University of Edinburgh centralised storage When ready for analysis samples will be defrosted at room temperature for 60-120min, mixed well with vortex then centrifuged. Laboratory staff will aliquot 320 µl from the original tubes to Eppendorf tubes and set in the centrifuge basket before spinning at 3000 G, 6 degrees for 10 minutes.

The ARCHITECTSTAT high-sensitive cardiac troponin I (Troponin) assay (Abbott Laboratories, Abbott Park, IL, USA) will be used for sample analysis in this study and has a limit of detection of 1.2 ng litre^{-1} and an inter-assay coefficient of variation of <10% at 4.7 ng litre^{-1}. The mean concentration for a healthy reference population is 1.6 (3.1) ng litre^{-1}, and the 99th percentile URL for the whole population is 26 ng litre^{-1} (females, 16 ng litre^{-1}; 34 males, ng litre^{-1}).

Depending on time, biomarker required and availability of storage, samples will be stored for bona fide research purposes for a period 5 years after the study end date.

7 DATA COLLECTION

7.1 DATA COLLECTION

The following data will be collected from participants in RESULT-Hip.

Screening Data

Anonymised screening data will be recorded on screening logs and entered onto the database by research teams at site. This data will be used to generate a CONSORT diagram at the end of the trial

At enrolment (pre-consent)

- Participant Name
- Participant Contact details
- Personal Consultee Name and Contact details (if appropriate)
- date of admission
- Date of birth

At Randomisation:

- Age
- Gender
- Pre-existing cardiovascular disease
- haemoglobin

At Baseline or as soon as available afterwards.

- CHI or NHS number
- ethnicity (using British Census 2021 categories)
- residential status (own home/sheltered housing, residential care, nursing care)
- pre-fracture mobility status (see NHFD proforma APPENDIX D)
- Abbreviated Mental Test Score (AMTS) or AMT4
- fracture type (see NHFD proforma APPENDIX D)
- date of surgery
- ASA-PS
- type of anaesthesia (general, spinal, other regional)
- operation performed
- duration of surgery
- preoperative haemoglobin
- haemoglobin after surgery (PACU, Recovery Ward, Ward on operative day)
- number of allogeneic units of blood transfused intraoperatively
- G number as a record of all red cell transfusions administered
- Use of blood sparing management technology or therapies
- history of dementia
- pre-existing malignancy
- pre-existing cardiovascular disease

- cardiovascular risk factors (vascular disease, diabetes, hypertension, kidney disease)
- presence of atrial fibrillation
- cardiac medications
- anticoagulant and anti-platelet medications
- Creatinine and eGFR
- Troponin
- 12-lead electrocardiogram
- Nottingham Hip Fracture Score (33)
- Rockwood Clinical Frailty Scale
- 4 'A's Test (4AT) for delirium
- EQ-5D-5L

Post randomisation **the following will be collected:**

- Haemoglobin and U&E's, one measurement days 2 – 5. Where possible these will be timed with existing blood sampling.
- pre and post transfusion haemoglobin (each transfusion episode, according to transfusion guidelines)
- Two blood samples for troponin for batch analysis in Edinburgh
- ECG on the 3rd day (window day 2 – 5) following randomisation
- Number of units of blood transfused following first time of Hb less or equal to 90 g. L^{-1}
- Volume of blood transfused (ml) following first time of Hb less or equal to 90 g. L^{-1}
- G number as a record of all red cell transfusions administered
- AKI (KDIGO criteria) (from review of paper and electronic case notes)
- Delirium (via 4AT) twice in days 1 - 5 following randomisation (supplemented by review of paper and electronic case notes)
- All post-operative complications using Hip Fracture Post-Operative Morbidity Survey (Appendix A)
- Episodes of chest pain days 0 – 3

At 30 days post randomisation **the following will be collected:**

- G number as a record of all red cell transfusions administered
- length of hospital stay
- Major adverse cardiac events (MACE) including myocardial infarction (from review of paper and electronic case notes
- New MINS
- Copy of any non-trial cardiac investigations carried out locally e.g. angiogram, echocardiograph uploaded to CRF
- New stroke*
- New pulmonary embolus*
- All complications (Appendix A)
- AKI using KDIGO definitions

- Mortality
- EQ-5D-5L
- Health services utilisation (HE questionnaire)

At 120 days post randomisation **the following will be collected:**

- Acute hospital discharge destination
- Emergency readmission
- Readmission specialty and location
- Mortality
- Cause of death (if applicable)
- Re-operation
- Total number of hospital, ICU, HDU bed days.
- Place of residence (using NHFD)
- Mobility (using NHFD)
- EQ-5D-5L
- Health services utilisation (HE Questionnaire)

*Definition of stroke or pulmonary embolus is “confirmation by the clinical team that the patient has had a stroke or pulmonary embolus”.

7.2 SOURCE DATA

Source documents will include:

- Paper medical records
- Electronic medical records
- Electronic laboratory results
- Paper electrocardiographs
- EQ-5D-5L and HE questionnaires
- Death certificates

7.3 SOURCE DATA DOCUMENTATION

Data will be inputted by the local research team directly into the electronic database or will be collected on case report forms and paper questionnaire proformas before being entered into the secure, trial specific database using REDCAP: Research Electronic Data Capture (Vanderbilt University, USA). This is a secure, password protected platform, hosted on University of Edinburgh servers.

8 DATA MANAGEMENT

8.1 PERSONAL DATA

The following personal data will be collected as part of the research:

- Participant name, address, telephone number and participant representative details (if appropriate), will be recorded on a contact details CRF and stored securely within the ECTU study database to facilitate central follow up by the research team at each site. Access to contact details data will be minimised and only accessible to those with delegated responsibility. Personal data will be stored for a minimum of 5 years after the study end date.

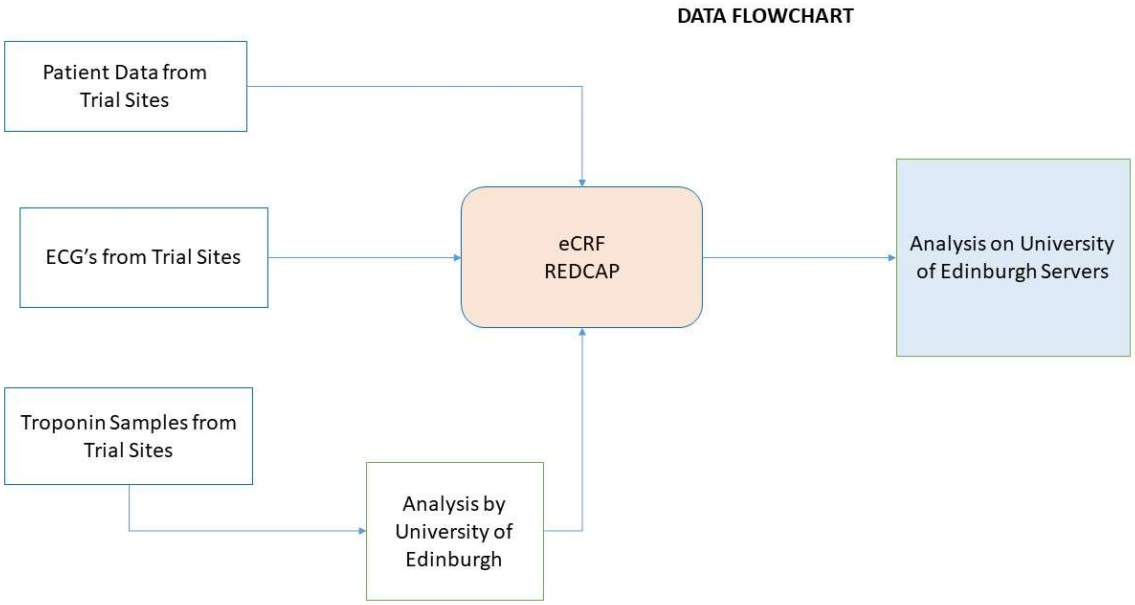
- Patient initials will be recorded on screening logs and stored securely within the ECTU REDCAP database for the purpose of monitoring and reporting patient flow through the trial via the production of a CONSORT diagram.

- Patient gender, date of birth and National Health Service (NHS) number, hospital number, Community Health Index (CHI) number, or other unique hospital identifier will be recorded and stored securely within the ECTU REDCAP database for the purposes of statistical analysis and correct identification of patients by research teams for follow up.

- Personal data will be stored at site by research teams on NHS computers (desktop and laptop). Computers will be password protected and kept in locked offices. All paper files containing personal data will be held in a secure location according to local NHS/University policies, as applicable.

- Personal data entered onto the ECTU REDCAP database will be hosted securely on University of Edinburgh servers. Only approved delegated members of the local research team or wider study team will have access to personal data.

Baseline and follow up data to 120 days, including de-identified scans of ECG's and other cardiac investigations e.g. angiogram , will be collected by the local research team at each site and entered onto /uploaded to the ECTU REDCAP database. The local research team can only view the records of patients from their own centre.



8.2 TRANSFER OF DATA

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation unless part of the trial. or without specific prior ethical approval.

Blood samples for troponin analysis will be transferred from sites by secure courier to the University of Edinburgh for analysis.

8.3 STUDY DATABASE

The study database will be created and maintained by ECTU. The database will be compliant with the relevant regulations and Sponsor Standard Operating procedures (SOPs) Trained and delegated members of the research team will be given password protected logins to the database. The data will be stored on a secure server in the University of Edinburgh

8.4 ARCHIVING OF STUDY DATA

All trial related and source documents should be archived for three years after the study end date in accordance with the Sponsor's archiving policy,

8.5 ARCHIVING OF CENTRAL DATA

All trial related documents will be archived for three years in accordance with the Sponsor's archiving policy unless an alternative longer archiving period is specified by the sponsor or the funder.

8.6 DATA CONTROLLER

The University of Edinburgh and NHS Lothian are joint data controllers along with any other. entities involved in delivering the study that may be a data controller in accordance with applicable laws

8.7 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Sample size calculations were informed by our pilot studies, the 2019 NHFD Annual Report, the FOCUS trial (US-based pre-2010), other observational studies and expert opinion. In people with hip fracture, we estimate 30-day all-cause mortality will be 7%, rates of MACE will be 10% and rates of new MINS will be 20%. Note these rates reflect 'whole population' outcome rates and are expected to underestimate rates seen in the proposed trial population (enriched by anaemia status which is associated with higher death and MACE event rates).

Rates of cardiac injury and death in anaemic participants are likely to be higher (as in our pilot trial), and components will occur concurrently in some participants. Conversely, routine Troponin/ECG measurement may increase MI detection compared to previous studies. Overall, we estimate a population 'usual care' MACE rate (including death) of 10% at 30 days. We estimate the rate of new MINS in this population to be 20% based on pilot data. Based on clinical consensus among UK opinion-leaders/experts, we consider an absolute risk reduction (ARR) of 5% in the primary outcome to be a realistic meaningful effect size that would change practice (33% Relative RR). Importantly, this would represent a number needed to treat (NNT) of 20 for every patient receiving liberal transfusion to avoid a death or MACE or new MINS outcome compared to the restrictive group.

We recognise limitations of a composite primary outcome treated as a binary (yes/no) indicator, because components treated equally may have differing importance to patients and clinicians. Importantly, nonfatal and/or less severe parts of the composite may occur more frequently and might dominate overall event rates. We will address this with an ordinal ranking of the possible outcomes at 30 days (1 best; 6 worst) according to severity/importance:

[1] No death, no MACE, no new MINS
[2] No death, no MACE, but new MINS.
[3] No Death ≥1 MACE
[4] Death, no MACE, no new MINS;
[5] Death, plus new MINS
[6] Death plus ≥1 MACE.

We will also report rates of MACE components and new MINS separately.

Thus the assumed 30 day mortality rate is 7%, MACE at 30 days is 10%, and rate of new MINS is 20%. To detect a 30% RRR (corresponding to a log-odds-ratio of approximately 0.64) and assuming proportional odds (34) between the liberal and restrictive groups, we require a sample size of 379 participants in each arm, using a Wilcoxon-Mann-Whitney rank-sum test with a 5% two-sided significance level and 80 % power. Allowing for a 10% dropout rate, we propose to recruit 421 participants per group. Total sample size 842 participants.

9.2 PROPOSED ANALYSES

All statistical analyses will be pre-specified in a comprehensive statistical analysis plan agreed prior to database lock. The plan will be authored by the study statistician and agreed by the independent study oversight committees.

The primary outcome will be analysed using a ranking process for each of its components i.e., they will be ranked according to the possible outcomes at 30 days (1 best: 6 worst) according to severity/importance:

[1] No death, no MACE, no new MINS
[2] No death, no MACE, but new MINS
[3] No Death ≥1 MACE
[4] Death, no MACE, no new MINS
[5] Death, plus new MINS
[6] Death plus ≥1 MACE

These ranks will form the basis of the primary analysis using the Wilcoxon-Mann-Whitney rank sum test, under an intention to treat principle, as appropriate for a superiority design. We will also consider a potentially more powerful analysis using Koch's non-parametric ANCOVA, adjusting for the stratification variables included in the randomisation i.e., centre, age (<80 vs. ≥ 80 years) and pre-existing CVD. If appropriate, analyses will be adjusted for site as a random effect. On review of baseline characteristics, the extent of the association between pre-existing CVD and anticoagulant use will be assessed and, if it is found that anticoagulant use is not strongly associated with pre-existing CVD, then it will be included as an additional covariate in all adjusted analyses. As a secondary analysis, we will assess the primary outcome using an ordinal logistic mixed effects regression. We will explore the robustness of the findings to any missing data using multiple imputation according to Rubin's approach under an assumption of

missing at random. We do not expect the level of missing data to be high, and hopefully less than the assumed 10%, making an approach assuming informative missing-ness unlikely to be either necessary or feasible.

To address the possibility that any component of the primary outcome (particularly Atrial fibrillation (AF) or new MINS) is much more prevalent in the trial than expected and dominates the primary composite outcome, we propose the following: all the individual components of MACE and new MINS will be reported as secondary outcomes and an a priori sensitivity analysis is undertaken with the AF and new MINS components of the primary outcome removed. This will be pre-specified in the statistical analysis plan when developed and proposed as a secondary analysis.

As a supplementary analysis based on the primary outcome, we will maximise the value of information from the RESULT-HIP trial by using the confidence distribution approach as outlined in Marschner 2024 [35] This approach will be used to make confidence probability statements about the treatment effect that are analogous to posterior probability statements generated from a Bayesian analysis, which will aid interpretability of the trial results. In particular, we will estimate the (confidence) probability that the true common odds ratio is greater than 1, 1.1 and/or 1.2, based on the results output from the ordinal regression analysis.

Secondary outcomes will be analysed using logistic regression for binary outcomes and linear regression for normally distributed continuous outcomes. Continuous outcomes that are not normally distributed will be analysed using appropriate non-parametric techniques. Time to event data will be analysed using an appropriate survival model (e.g., Cox proportional hazards).

Pre-specified sub-group analyses will explore effects in relation to gender, age (<80 vs. ≥ 80 years), presence of pre-existing CVD and use of anticoagulant and antiplatelet drugs. These will be analysed as per the primary outcome but including a covariate*treatment interaction.

No interim analysis is planned.

9.3 ECONOMIC EVALUATION

Full details of the economic evaluation will be specified in a comprehensive Health Economic Analysis Plan (HEAP) (36) authored by the study health economist(s), and signed off by the Chief Investigator prior to analysis.

Two forms of analyses will be undertaken: A cost-consequence analysis (CCA) of the 120-day observed trial period, and longer-term economic modelling.
NHS and PSS (personal social services) will be collected, including details of the initial surgical admission (including complications and recovery period), readmissions, A&E, a, outpatient admissions, any ongoing care packages related to recovery, calls to NHS24/NHS Direct, and primary care. These will be combined with standard UK price weights (37, 38) to generate costs

with base year selected as the latest year for which at least 1 participant provides data, and price weights are available. Most of the resource use will be extracted retrospectively from medical records at 120 days, though some top-up self-report may be necessary for minor aspects, particularly around primary care.

The CCA will present these as a profile of NHS and PSS utilisation and cost as additional contextual information alongside health outcomes (including the EQ-5D-5L) without attempting to combine data and estimate Incremental cost per Quality Adjusted Life Years (QALY). This will comprise of univariate mean EQ-5D-5L scores, rates of resource use, and associated costs (type and total) presented for each trial arm alongside differences in means (intervention minus control) and associated 95% confidence intervals. Missing data will be imputed using appropriate techniques depending on degree of missingness, likely multiple imputation by chained equations (which is considered gold standard in this area). (39)Though we note that most important cost factors such as inpatient readmission and care packages will be obtained from medical records and are therefore anticipating high levels of completeness.

The formal assessment of long run cost-effectiveness will be undertaken using decision analytic modelling to account for potential health and cost implications of transition to care home, other rehabilitation programs or care in the community.
The model structure will be developed with input from clinical experts. Its parameters will be populated using trial data (including costs and EQ-5D-5L where appropriate), targeted (non-systematic) literature searches, or as a last resort, through formal expert opinion elicitation. To maximise UK policy relevance, the model will follow NICE reference case recommendations including: Adoption of an NHS and personal social service(PSS) costing perspective; cost-utility approach (results presented in terms of incremental cost per QALY calculated from EQ-5D-5L data); discount rate of 3.5% for both costs and QALYs; and the use of probabilistic sensitivity analysis (PSA), most likely generated via a method of moments approach. (44) Choice of primary analysis cost per QALY threshold and EQ-5D-5L scoring algorithm will be selected to match NICE preferences at time of data lock to allow for potential changes in recommendations between trial start and analysis.

10 ADVERSE EVENTS

Adverse Event (AE) and Serious Adverse Event (SAE) reporting will follow the ACCORD SOP for non-CTIMP trials (CR006).

Transfusion Related Adverse Events or Reactions and Serious Transfusion Related Adverse Reactions will be recorded in accordance with the definitions of SHOT (Serious Hazards of Transfusion), revised December 2019. Imputation of any transfusion related AE, AR or SAE will also be assessed according to the definitions given within the SHOT guidance (see Appendix B)

https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Definitions-update-10.01.20-FINAL.pdf

10.1 DEFINITIONS

10.1.1 Adverse Event (AE)

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention.

10.1.2 Adverse Reaction (AR)

Any untoward and unintended response that has occurred due to the intervention.

10.1.3 Transfusion Related Adverse Reaction (AR) or Event

Any untoward and unintended response to a transfused blood component.

10.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) OR Serious Transfusion Related Adverse Reaction

A serious adverse event (SAE) is defined as an untoward occurrence that:

- results in death.
- is life-threatening.
- requires hospitalisation or prolongation of existing hospitalisation.
- results in persistent or significant disability or incapacity.

An SAE occurring to a research participant should be investigated at a local level by the local PI and then reported to the CI and sponsor when, in the opinion of the local PI, the event was either

- Related – it resulted from administration of any of the research procedures

And / or

- Unexpected – the type of event is not listed in the protocol as an expected occurrence.

10.2 IDENTIFYING AND REPORTING AEs AND SAEs

10.2.1 Assessment of Transfusion Reactions

As mentioned above, transfusion related reactions will be assessed in accordance with the definitions and imputability as set out by SHOT but will also be recorded as an AE on the trial database. All Serious Transfusion Related Adverse Reactions will be recorded as part of the trial data collection process.
Examples include:

- Incorrect or incompatible blood transfusion
- Serious adverse reactions to blood transfusion including (but not exclusively):
- Allergic/febrile transfusion reactions occurring at any time up to 24 hours following a transfusion of a blood component

- Acute or delayed Haemolytic transfusion reaction
- Post transfusion Purpura (thrombocytopenia)
- Transfusion associated graft vs host disease
- Transfusion associated circulatory overload
- Transfusion associated dyspnoea
- Transfusion associated acute lung injury
- Transfusion transmitted infection

10.2.2 AEs and SAEs that do not require reporting

This study enrols older, anaemic participants who have undergone major emergency surgery and it is expected that many of these participants will suffer medical complications, with consequences up to and including death. Only complications considered by the local PI, or delegated authority, to be *related to the use of study procedures* and not a typical and frequently reported complication of admission to hospital with hip fracture should be reported as AEs. Complications that fall into this category but are defined as endpoint events in protocol section 1.4, e.g. cardiac events, will be recorded as outcome events (whether they are deemed to be related to the use of study procedures or not). Common hospital complications of hip fracture are listed in the table below:

Common complications of admission to hospital with hip fracture
Electrolyte disturbance, including, but not limited to hypo or hypernatremia, hypo or hyperkalaemia.
Anaemia*
AKI
Delirium*, acute confusional state
Cognitive impairment, chronic or acute
Venous thromboembolic Disease
Respiratory: Chest infection pneumonia, sepsis
Cardiac*: myocardial infarction, acute coronary syndrome, atrial fibrillation, another arrhythmia, *
Cerebrovascular: Stroke or transient ischaemic attack
Infection*
Urinary infection
Pressure sores
Skin ulcers
Immobility
Fall
Death

Complications of surgical fixation of fractured hip
Wound complications
Impaired wound healing
Haematoma
Mechanical malfunction [dislocations, cutting-out, refracture]
Infections
non/malunion

* Complications that are recorded as part of the outcome measures are detailed in the protocol.

10.2.3 Duration of AE and SAE reporting

AE and SAE reporting will start from the time of randomisation in the trial. AEs and SAEs will only be reported during the intervention period, namely from randomisation until the time of acute hospital discharge or 30 days whichever is soonest. Important events that might constitute AEs and SAEs that may plausibly be associated with the intervention are being recorded as part of trial follow up data collection at 120 days post-randomisation.

10.2.4 Reporting and follow up of AEs and SAEs

AE and SAE data will be recorded by the Investigator(s) (or a member of the research team with delegated responsibility to do so) on the Case Report Forms (CRF) and/or SAE report form. Investigators will record all AEs in the AE log in a timely fashion (usually at the time of detection). AEs and SAEs will be followed up until outcome of recovered, recovered with sequelae or death of the study participant.

10.3 ASSESSMENT OF AEs

Each AE must be assessed for seriousness, causality, severity, and expectedness by the Principal Investigator (PI) or another suitably qualified physician in the research team who is trained in recording and reporting AEs and who has been delegated this role. During PI absences appropriately qualified, experienced, and trained site staff may assess causality and report SAEs if they have been delegated this responsibility on the delegation log by the PI.

10.3.1 Assessment of seriousness

The Investigator will assess seriousness (as defined in section 11.1).

10.3.2 Assessment of Causality

The Investigator will assess whether the AE is likely to be related to the study intervention according to the following definitions:

Unrelated: where an event is not considered to have occurred because of the study intervention.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication, or temporal relationship make it possible that the AE has a causal relationship to the study intervention.

Where there are two assessments of causality (e.g., between PI and Chief Investigator (CI)), the causality assessment by the Investigator cannot be downgraded. If there is a difference of opinion, both assessments will be recorded, and the "worst case" used for reporting purposes.

10.3.3 Assessment of Expectedness

If the AE is judged to be related to the study intervention, the Investigator will assess expectedness.

- *Expected* The type of event is expected within the study population or intervention
- *Unexpected* The type of event was not listed in the protocol or documents/literature as an expected occurrence

10.3.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE, and this should be recorded on the CRF or SAE form according to the following categories:

Mild: an event that is easily tolerated by the study participant, causing minimal discomfort, and not interfering with everyday activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities

Severe: an event that prevents normal everyday activities.

*The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', as defined in section 10.1, which is a regulatory definition based on study participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

10.4 REPORTING SAEs TO THE SPONSOR (University of Edinburgh and NHS Lothian)

Any AE that is assessed as an SAE is subject to expedited reporting requirements to the Sponsor. The SAEs described in 10.2.1 do not require expedited reporting to the sponsor. The Investigator is responsible for reporting SAEs to ACCORD within 24 hours of becoming aware of the event.

SAE reports will be emailed as a .pdf file to Safety@accord.scot SAE reports will be complete as far as possible and will be signed and dated by the Investigator. The SAE does not require to maintain blinding as this is an unblinded trial. The Research Governance Coordinator, or designee, will complete and return the Cover Sheet and Return Receipt or send an email to confirm receipt of the SAE report within 1 working day. If this email is not received within 1

working day of sending the report to ACCORD, the Investigator must email safety@accord.scot to check that the report has been received by ACCORD.

All copies of SAE reports emailed to ACCORD, and any follow-up information and correspondence will be kept by the Investigator in the Investigator Site File (ISF) and by the Sponsor in the Sponsor File or Trial Master File (TMF).

ACCORD will report SAEs, as required, to the Chief Investigator/Trial Manager upon request.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.
Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11.3 PUBLIC ENGAGEMENT

A patient Personal and Public Involvement (PPI) representative is a co-applicant and will attend the trial management group throughout the trial to ensure the views and opinions of service users, carers and the public are represented. In addition, a wider PPI group will be consulted on the protocol prior to submission for ethical approval, and specifically will be asked to review patient and patient-representative materials including the Patient (or representative) Information Leaflet and consent forms.

The views of PPI representatives will be sought during interpretation of the study results as appropriate.

11.4 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group, consisting of selected grant holders, a trial manager and trial nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility, and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

11.5 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial and advise the investigators as required. The TSC will include an independent Chair, at least one independent clinician, at least one independent methodologist, and at least one independent PPI representative. The terms of reference of the Trial Steering Committee, the draft template for reporting, and the names and contact details are detailed in CR015 DMEC & TSC Charters.

11.6 DATA MONITORING AND ETHICS COMMITTEE

An independent Data Monitoring and Ethics Committee (DMEC) will be established to oversee the safety of participants in the trial. The DMC will comprise three individuals and include at least one statistician and one clinical content expert. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMEC & TSC Charters.

The DMEC Charter will be signed by the appropriate individuals prior to the trial commencing.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).
Before the study can commence, all required approvals will be obtained, and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

12.2.2 Study Site Staff

The Principal Investigator must be familiar with the protocol and the study requirements. It is the Principal Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (SFs.)

12.2.5 GCP Training

For non-CTIMP (i.e., non-drug) studies all researchers are encouraged to undertake GCP training to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or

other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) about the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified, and re-identification is not likely to take place

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being recruited into an amended protocol.

13.2 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e., protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

13.2.1 Definitions

A protocol **deviation** is any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.

A protocol **violation** is a deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

For the purpose of the trial, any non-compliance with the allocated RBC transfusion intervention, such as failure to transfuse in response to a trigger Hb and/or administering transfusion when the Hb concentration does not indicate transfusion, should be reported as a protocol deviation. For transfusion decisions, a deviation will be defined as failure to follow the allocated transfusion intervention following an Hb measurement within 48 hours following the Hb measurement.

In the restrictive group, any transfusions administered when the Hb is >75g L^{-1} will be reported as a deviation.

The following scenarios are protocol deviations of particular interest.

1. Transfusion of red blood cells at Hb above the predefined transfusion trigger.
2. Failure to transfuse within 48 hours after the protocol requires a red cell transfusion according to the allocated trial group.
3. Transfusion without checking haemoglobin level.
4. Major haemorrhage: It may be necessary for physicians to transfuse participants with red blood cells in emergency or life-threatening situations, for example in a major haemorrhage or uncontrolled bleeding. These transfusions will be recorded together with the reasons for the transfusion.

13.2.2 Recording and reporting protocol deviations and violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot. Protocol deviations of particular interest will also be recorded on the study database.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.6 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study will reside with the study team.

14.1.1 Reporting and publication

Results of the trial will be posted on the ISRCTN registered clinical trial website. The trial Chief Investigator and co-investigators will oversee decisions around presentation of results to scientific and clinical meetings, public/press releases, and social media notifications. The trial data will be published in peer-reviewed journals. The decisions surrounding publication will be made by the Chief Investigator and co-investigator.

14.1.2 Data Sharing

Consent will be sought from participants to permit sharing of anonymised data with funders and collaborators or published on publicly available resources as appropriate.
Co-investigators will have the right to access the final data set for the purpose of additional analyses that are consistent with the consent provided by participants.
Following publication of the primary paper, a de-identified individual participant data set will be submitted to a data archive for sharing purposes. Access to this data set will be under a controlled access model in line with ECTU policies at that time.

15 REFERENCES

1. Cooper C, Campion G, Melton LJ, . Hip fractures in the elderly: a world-wide projection. 1992. p. 285-9.
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16 APPENDIX A DEFINITION OF COMPLICATIONS

16.1 Assessment of Complications

All postoperative complications will classified using the Hip Fracture Postoperative Morbidity Survey (38):

Morbidity type	Criteria definition: Presence of one or more of the following:
Pulmonary	The patient developed a new requirement for oxygen or respiratory support;
Infectious	Currently on IV antibiotics; Has had a temperature of >38℗C in the last 24 hr; *Has a white cell count level requiring in hospital review or treatment;
Renal	Presence of oliguria <500 mL/24 hr; Increased serum creatinine (>30% from preoperative level); New urinary catheter in situ;
Gastrointestinal	Unable to tolerate an enteral diet for any reason including nausea, vomiting, and abdominal distension (use of antiemetic); *Diarrhoea *New poor appetite causing poor oral intake
Cardiovascular	Diagnostic tests or therapy within the last 24 hr for any of the following: (1) new MI or ischemia, (2) hypotension (requiring fluid therapy >200 ml/hr or pharmacological therapy), (3) *dizziness - significant postural hypotension on sitting or standing up (4) cardiac arrhythmia that requires treatment or further investigation, (5) pulmonary oedema, (6) thrombotic event (requiring anticoagulation).
Neurological	New focal neurological deficit, confusion/ delirium, coma.
Haematology	Requirements for any of the following within the last 24 hr: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate.
Wound	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organism; *Leaky wound requiring frequent dressing change
Pain	New and/or exacerbated postoperative pain significant enough to require any of the following: parenteral OR *oral opiates and/or continuing of additional analgesia; *pain limiting sitting up in bed or out on the chair.
*Endocrinology	*Difficult to control diabetes- hypoglycaemia or hyperglycaemia that requires specialist input
*Assisted Ambulation	*A new or escalated postoperative requirement for mobility assistance with two people and a walking aids; *Fatigue quickly limiting mobility.
*Psychological	*A new or exacerbated postoperative anxiety affecting mobility and /or self-care (coping at home).

Abbreviations: WCC, white cell count, IV, intravenous, MI, myocardial infarction, * New domains and criteria definitions.

16.2 Assessment of Cardiac Complications

Myocardial infarction: Any cardiac ischaemic event fulfilling 4th Universal Definitions for Myocardial Infarction

Myocardial Injury after Non-Cardiac Surgery: Troponin elevation above the assay upper reference limit within 30 days of randomisation 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.

16.3 Assessment of Acute Kidney Injury

Acute kidney injury will be staged if KDIGO criteria for either serum creatinine or urine output are met:

Stage	Serum creatinine	Urine output
1	1.5-1.9x increase from baseline OR absolute increase of 26.5 micromol/L	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9x increase from baseline	<0.5 ml/kg/h for >12 hours
3	3.0 x increase from baseline OR increase in serum creatinine to 353.6 micromol/L OR need for renal replacement therapy	<0.3 ml/kg/h for > 24 hours OR Anuria > 12 hours

16.4 Assessment of Delirium

Delirium should be assessed using the 4AT score and will be considered to be present if 4AT≥4 (see Appendix C).

17 APPENDIX B – SERIOUS ADVERSE TRANSFUSION RELATED EVENTS

Definitions of transfusion related SAEs are per the NHS Blood and Transplant "Serious Hazards of Transfusion" (SHOT) available at

http://www.shotuk.org/wp-content/uploads/SHOT-Definitions-Jan-2016-1.pdf

Expected Red Blood Cell Transfusion reactions

Acute transfusion reactions (ATR) are defined (SHOT Report, 2012) as those occurring at any time, up to 24 hours following a transfusion of blood or components.

- Anaphylactic reactions
- Moderate allergic reactions
- Hypotensive reactions
- Severe febrile reactions
- Mixed febrile/allergic reactions
- incorrect component being transfused
- haemolytic reactions
- transfusion-related acute lung injury (TRALI)
- transfusion-associated circulatory overload (TACO)
- transfusion-associated dyspnoea (TAD)
- bacterial contamination

18 APPENDIX C – DELIRIUM ASSESSMENT USING 4AT

[1] ALERTNESS

This includes patients who may be markedly drowsy (e.g., difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	0
Mild sleepiness for <10 seconds after waking, then normal	0
Clearly abnormal	4

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	0
1 mistake	1
2 or more mistakes/untestable	2

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December."
To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	0
	Starts but scores <7 months / refuses to start	1
	Untestable (cannot start because unwell, drowsy, inattentive)	2

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (e.g., paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	0
Yes	4

---

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

GUIDANCE NOTES

Version 1.2. Information and download: www.the4AT.com

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more *suggests* delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated *solely on observation of the patient at the time of assessment*. Item 4 requires information from one or more source(s), e.g., your own knowledge of the patient, other staff who know the patient (e.g., ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, "Are you concerned about anything going on here?"; "Do you feel frightened by anything or anyone?"; "Have you been seeing or hearing anything unusual?"

19 APPENDIX D NATIONAL HIP FRACTURE DATABASE DEFINITIONS

Royal College of Physicians | Falls and Fragility Fracture Audit Programme

National Hip Fracture Database - Dataset Specification v10A (2017)

(Applicable to patients admitted from 1 April 2017)

1. Patient information

		Patient ID / Hospital number K
First name	**Surname**	**NHS / CHI number B M**
Date of birth B M	**Sex M**	**Patient's post code M**
__ __ / __ __ / __ __ __ __	□ Male □ Female	
CCG B		

2. Admission

Hospital in which fracture is first identified	**Residence before this hospital admission M**
	□ Own home/sheltered housing □ Residential care □ Nursing care
Presentation with a hip fracture via A&E M	**Date & time of presentation to A&E or Trauma Team B M**
□ Yes □ No – already inpatient on this hospital site □ No – already inpatient in another hospital site of this Trust □ No – already inpatient in another Trust	__ __ / __ __ / __ __ __ __ __ __ : __ __
Admission date/time orthopaedic/orthogeriatric ward M	**Nerve block in A&E or ward before arrival in theatre suite**
__ __ / __ __ / __ __ __ __ __ __ : __ __ □ Never admitted to orthopaedic/orthogeriatric ward	□ Yes □ No

3. Assessment

Side of fracture K	**Pre-fracture mobility M**
□ Left □ Right	o Freely mobile without aids o Mobile outdoors with one aid o Mobile outdoors with two aids or frame o Some indoor mobility but never goes outside without help

	o No functional mobility (using lower limbs) o Unknown
Abbreviated Mental Test Score (AMTS) – pre op **B**	
_____ / 10 □ Not done/patient refused	
Type of fracture **M**	**Pathological** **M**
□ Intracapsular – displaced □ Intracapsular – undisplaced □ Intracapsular – unable to diagnose subtype □ Intertrochanteric – grade A1/A2 □ Intertrochanteric – grade A3 (including reverse oblique) □ Intertrochanteric – unable to diagnose subtype □ Subtrochanteric *Please note that selecting the correct fracture type affects the measurement of compliance with NICE guidance.*	□ Atypical bisphosphonate type subtrochanteric fracture □ Malignancy □ No □ Unknown **Nutritional risk assessment performed on admission** **B M** o Yes – assessment indicates malnourished o Yes – assessment indicates at risk of malnutrition o Yes – assessment indicates normal o No

4. Surgery *(Consider using a theatre data collection sheet to improve data quality)*

ASA grade **M**	
□ 1. A normal healthy patient □ 2. A patient with mild systemic disease □ 3. A patient with severe systemic disease □ 4. A patient with severe systemic disease that is a constant threat to life □ 5. A moribund patient who is not expected to survive without the operation □ Unknown	
Operation performed **B M**	**Date & time of primary surgery** **B M?**
□ Internal fixation - Sliding Hip Screw □ Internal fixation - Cannulated screws □ Internal fixation - IM nail (long) □ Internal fixation - IM nail (short) □ Arthroplasty - Unipolar hemi (uncemented - uncoated) □ Arthroplasty - Unipolar hemi (uncemented - HA coated) □ Arthroplasty - Unipolar hemi (cemented) □ Arthroplasty - Bipolar hemi (uncemented - uncoated) □ Arthroplasty - Bipolar hemi (uncemented - HA coated) □ Arthroplasty - Bipolar hemi (cemented) □ Arthroplasty - THR (uncemented - uncoated) □ Arthroplasty - THR (uncemented - HA coated) □ Arthroplasty - THR (cemented) □ Arthroplasty - THR hybrid □ Other □ No operation performed	__ __ / __ __ / __ __ __ __ __ __ : __ __ **Reason if delay > 36 hours** **M?** □ No delay - surgery < 36hrs □ Awaiting orthopaedic diagnosis/investigation □ Awaiting medical review/investigation or stabilisation □ Administrative/logistic - awaiting space on theatre list □ Administrative/logistic - cancelled due to theatre over-run □ Other □ Unknown
Type of anaesthesia **M?**	**Nerve block administered as part of operative anaesthesia** **M?**
□ GA only	□ Yes

□ GA + spinal anaesthesia □ GA + epidural anaesthesia □ SA only □ SA + epidural (CSE) □ SA + sedation □ SA + sedation + epidural □ Other	□ No
Grade of senior surgeon present in operating room M?	**Grade of senior anaesthetist present in operating room M?**
□ Consultant □ SAS □ ST3+ □ Below ST3 □ Unknown	□ Consultant □ SAS □ ST3+ □ Below ST3 □ Unknown

5. Post surgery / further assessments (where applicable)

Delirium assessment (in the week following surgery) B M?

□ Not done/patient refused

				Score / Total
Alertness	*0 (Normal)*	*4 (Abnormal)*		/ 4
AMT4	*0 (No mistakes)*	*1 (One mistake)*	*2 (Two mistakes)*	/ 2
Attention	*0 (No mistakes)*	*1 (One mistake)*	*2 (Two mistakes)*	/ 2
Acute change	*0 (No change)*	*4 (Change)*		/ 4
			Total	/ 12

Assessed by physiotherapist on the day of or day after surgery B M?	**Mobilised on day of or day following surgery M?**
□ Yes □ No	□ Yes - physiotherapist □ Yes - other ward staff □ No

Geriatrician grade B M	**Date & time assessed by geriatrician B M?**
□ Consultant □ SAS □ ST3+ □ Not seen	__ __ / __ __ / __ __ __ __ __ __ : __ __
Specialist falls assessment B M	
□ Yes □ No	
Bone protection medication B M	**Pressure ulcers M**
□ Started on this admission - oral medication □ Started on this admission - injectable medication □ Continued from pre-admission - oral medication □ Continued from pre-admission - injectable medication □ On no treatment - pending DXA scan or bone clinic assessment □ Assessed - no bone protection medication needed/appropriate □ No assessment or action taken	□ Yes □ No □ Unknown

6. Discharge

If the patient was admitted to an orthopaedic/orthogeriatric ward, then please complete the ward discharge section…	
Date of discharge from acute orthopaedic ward **M?**	**Discharge destination from acute orthopaedic ward** **M?**
__ __ / __ __ / __ __ __ __	□ Own home/sheltered housing □ Residential care □ Nursing care □ Rehabilitation unit – hospital bed in this Trust □ Rehabilitation unit – hospital bed in another Trust □ Rehabilitation unit – NHS funded care home bed □ Acute hospital □ Dead (please complete section 5a) □ Other
Date of final discharge from Trust **M**	**Discharge destination from Trust** **M**
__ __ / __ __ / __ __ __ __	□ Own home/sheltered housing □ Residential care □ Nursing care □ Rehabilitation unit – hospital bed in another Trust □ Rehabilitation unit – NHS funded care home bed □ Acute hospital □ Dead (please complete section 5a) □ Other □ Unknown
If the patient died while in hospital, either on the ward or in the care of the Trust, please complete this section…	
Death during hospital admission **M?**	
□ Died in spite of ongoing treatment, including an unsuccessful "crash call" □ Died following documented discussion of priorities for end of life care with the patient and appropriate members of their family □ Other	

Field markers

K = Key field. If missing or invalid data is entered, the record will be rejected.

B = Required for Best Practice Tariff. If missing or invalid data is entered, then record will not be counted for BPT.

M = Mandatory field. If missing or invalid data is entered, the record will remain in **draft** form.

M? = Becomes mandatory if applicable. For example: Surgery date becomes mandatory, if surgery is performed.

Follow-up at 120 days follows…

7. Follow-up at 120 days

Date patient contacted	__ __ / __ __ / __ __ __ __ or ☐ Patient could not be contacted
Residential status	☐ Own home/sheltered housing ☐ Residential care ☐ Nursing care ☐ Rehabilitation unit – hospital bed in this Trust ☐ Rehabilitation unit – hospital bed in another Trust ☐ Rehabilitation unit – NHS funded care home bed ☐ Acute hospital ☐ Dead ☐ Other ☐ Unknown
Post fracture mobility	o Freely mobile without aids o Mobile outdoors with one aid o Mobile outdoors with two aids or frame o Some indoor mobility but never goes outside without help o No functional mobility (using lower limbs) o Unknown
Bone protection medication	☐ Continues with same bone protection medication as on discharge ☐ Started on alternative bone protection medication ☐ Bone protection medication stopped or not started (for any reason)
Reoperation within 120 days of admission to A&E Note: Select most significant procedure only	☐ Reduction of dislocated prosthesis ☐ Washout or debridement ☐ Implant removal ☐ Revision of internal fixation ☐ Conversion to Hemiarthroplasty ☐ Conversion to THR ☐ Girdlestone/excision arthroplasty ☐ Surgery for periprosthetic fracture ☐ None ☐ Unknown

Notes

Five fields are no longer required for patients admitted from April 2017 (v10A dataset), but are still present on the web-form. These fields are still required for patients admitted before April 2017 (v10 dataset) for BPT purposes.

1.07	Ortho GMC	
1.08	Geri GMC	
1.09v8	Joint assessment protocol	
2.13v8	Post-op AMTS2	
5.03	Rehabilitation Assessment	

Consider using a theatre data collection sheet to improve data quality, available here: **www.nhfd.co.uk/theatre**

All data must be submitted electronically at: **www.nhfd.co.uk**

Users wishing to import data should refer to the import notes and specifications available on the website

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20 APPENDIX E CONSENT PROCESS IN DEVOLVED ADMINISTRATIONS