The clinical benefits and cost effectiveness and safety of haematopoietic interventions for patients with anaemia following major emergency surgery: a phase IV, multi-site, multi-arm randomised controlled trial: Peri-op Iron and Erythropoietin (EPO) Intervention Study (POP-I)

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Short title:	Perioperative Iron and EPO Intervention Study
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1. SYNOPSIS

Title	The clinical benefits and cost-effectiveness and safety of haematopoietic interventions for patients with anaemia following major emergency surgery: a phase IV, multisite, multi-arm randomised controlled trial: Peri-op Iron and Erythropoietin (EPO) Intervention Study.
Acronym	POP-I
Short title	Perioperative Iron and EPO Intervention Study
Chief Investigator	Iain Moppett – Professor of Anaesthesia and Perioperative Medicine
Primary Objective	To assess the clinical effectiveness of postoperative intravenous iron and intravenous iron plus a subcutaneous injection of an Erythropoiesis Stimulating Agent (ESA) compared to a usual care control group respectively, for the treatment of anaemia across two major patient groups who have had emergency surgery.
Secondary Objectives	1. To monitor safety of the interventions. 2. To conduct an internal pilot to evaluate recruitment, uptake and retention rates, sample size parameter estimates, clinician protocol adherence, safety, adherence to treatment allocation, completeness, and quality of data collection. 3. To assess the cost effectiveness/cost utility of postoperative intravenous iron and intravenous iron plus ESA compared to a usual care control group respectively, and impact on resource use and quality of life from a healthcare, social care and broader societal viewpoint.
Trial Configuration	Multisite, multi-arm, open-label, pragmatic randomised controlled trial with integral internal pilot and concurrent economic evaluation. The trial is predicated on two primary comparisons of (1) a monotherapy and (2) a combination therapy, compared with a single common control group (usual care) respectively, in a superiority hypothesis testing framework.
Setting	Approximately 40 acute care hospitals providing care to people with hip fracture or requiring emergency laparotomy in the UK.
Target population	Adults aged 60 years or over with mild or moderate anaemia (Hb 80–110g/l) after either hip fracture surgery or emergency laparotomy.
Sample size estimate	To detect a mean difference of 2 days in 'Days at Home at 30 Days' (DAH30) between an active treatment group and the usual care group, a total of 792 patients per group are required to achieve 90% statistical power. This is based on the following assumptions: a common standard

	deviation for DAH30 of 11, a two-sided 2.5% level of statistical significance (partitioned for two primary comparisons), and allowing for up to a conservative maximum of 5% non-collection of primary outcome data. The total sample size target is scaled up to 2,400 participants.
Number of participants	2,400 participants in total (800 participants in each of the three groups)

Eligibility criteria	Inclusion:
	• Age 60 years or older.
	• Hb 80–110g/l measured on any day between day 1 and day 10 after surgery.
	• Major non-elective surgery in the last 1 to 10 days: Patient will have undergone either Emergency Laparotomy as defined by National Emergency Laparotomy Audit (NELA) ***OR*** Fragility Hip Fracture surgery as defined by National Hip Fracture Database (NHFD).
	• Written informed consent from participant or legal representative.
	
	Exclusion:
	• Use of intravenous iron, darbepoetin or other ESAs in last 30 days.
	• Haematological diagnoses where iron overload is a risk (e.g., haemochromatosis or alpha-thalassaemia trait) or alternative treatments are indicated (e.g., haematological malignancies).
	• Acute uncontrolled infection as judged by the treating clinician (e.g. ongoing bacteraemia or non-resolving sepsis) or patient expected to be on non-prophylactic antibiotics for greater than 14 days.
	• Contraindication to thromboprophylaxis.
	• Direct contraindications to IMP:
	  ○ disturbances of iron, iron overload
	  ○ uncontrolled hypertension
	  ○ red cell aplasia
	  ○ decompensated / severe chronic liver disease (Child Pugh C)
	  ○ advanced cancer (metastatic and/or receiving chemo/radiotherapy)
	• Patient not expected to survive for 30 days.
	• Renal replacement therapy.
	• Immunosuppressive therapy for organ transplant.

Description of interventions	**USUAL CARE** (without additional anaemia therapy): All recruitment sites will provide care aligned to national standards and guidelines including: NICE CG124, National Hip Fracture Database (NHFD), Association of Anaesthetists (hip fracture); National Emergency Laparotomy Audit (NELA) (emergency laparotomy); Best Practice Tariff (emergency laparotomy and hip fracture). **IRON MONOTHERAPY:** Usual care plus intravenous Ferric Derisomaltose (approximately 20 mg/kg as a single dose before discharge). **COMBINATION IRON AND ESA:** Usual care plus intravenous Ferric Derisomaltose (as per IRON MONOTHERAPY) plus a subcutaneous injection of Darbepoetin (approximately 2 mcg/kg as a single dose before discharge).
Duration of trial	Overall trial duration: 4 years Duration of trial for individual participants: 120 days

Randomisation and blinding	Eligible participants will be randomised via a secure password-protected 24/7 website hosted by Nottingham Clinical Trials Unit. Allocation (ratio 1:1:1) will be assigned using a probabilistic minimisation algorithm balancing across the three groups on five important factors - recruiting site, type of surgery, age, sex, and postoperative haemoglobin concentration at randomisation.
Outcome measures	**Primary outcome** • Days at home up to 30 days after randomisation (DAH30) **Secondary outcomes** • Health-related quality of life assessed using EQ-5D-5L at Baseline, 30 days and 120 days • Days at home up to 120 days after randomisation (DAH120) • Self-reported walking performance (mobility) at 30 days and 120 days • Residential status reported at discharge, 30 days and 120 days • Complications at discharge, 30 days, and 120 days • Length of hospital stay • Mortality at hospital discharge, 30 days and 120 days
Statistical methods	The primary approach to between-group comparative analyses will be by intention-to-treat, without imputation of missing outcome data. The primary comparative analysis will employ generalised linear mixed effects regression modelling to compare DAH30 between groups (each active treatment group versus usual care respectively), adjusting for minimisation factors and including random effects to adjust for clustering within surgery type and recruiting site. We will present the difference in means, along with 95% confidence intervals for each primary comparison. If data for DAH30 show substantial departures from model assumptions, then alternative parametric distributions or non-parametric alternatives will be employed.
Health Economics	**Outcome** Health-related quality of life assessed using EQ-5D-5L at Baseline, 30 days and 120 days (self-reported) Days at home up to 30 days (DAH30) and 120 days (DAH120) after randomisation (self-reported) **Resource Use** Data collected will include the intervention resource use by surgical group. In addition, post inpatient costs will be collected to include detailed patient resource use on secondary care, primary care, social care, indirect patient costs (employment) and out of pocket expenses. **Analysis** If appropriate, the incremental cost effectiveness ratio (ICER) will be presented between the control group and the intervention groups. The costs and benefits will be analysed using the incremental Marginal Net Benefit (MNB) approach. Cost Effectiveness planes and cost effectiveness acceptability curves will be plotted between the control and the intervention groups.

2. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CDC	Centres for Disease Control
CI	Chief Investigator
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CRF	Case Report Form
CUA	Cost Utility Analysis
DAH30/120	Days at Home at 30 / 120 days
DAOH 30	Days alive and out of hospital at 30 days
DAP	Data Analysis Plan
DiRUM	Database of Instruments for Resource Use Measurement
DMC	Data Monitoring Committee
DMP	Data Management Plan
EOT	End of Trial
EPO	Erythropoietin
EBPOM	Evidence Based Perioperative Medicine
EQ-5D-5L	EuroQol 5 dimension, 5 level measure of quality of life
ESA	Erythropoiesis Stimulating Agent
GCP	Good Clinical Practice
HES-APC	Hospital Episode Statistics – Admitted Patient Care
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ISF	Investigator Site File
IMP	Investigational Medicinal Product
INMB	Incremental Net Monetary Benefit
MNB	Marginal Net Benefit
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Nottingham Clinical Trials Unit
NELA	National Emergency Laparotomy Audit
NHFD	National Hip Fracture Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute of Health Research Health Technology Assessment
PAG	Patient Advisory Group
PI	Principal Investigator at a local site
PIS	Participant Information Sheet
PLR	Personal Legal Representative
PPI	Patient and Public Involvement
PSSRU	Personal Social Services Research Unit
QoL	Quality of Life
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
R&D / R&I	Research and Development / Innovation department
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SSI	Surgical Site Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TABLE OF CONTENTS

3. TRIAL BACKGROUND INFORMATION AND RATIONALE

Anaemia after major, emergency surgery in older people is common and is associated with increased mortality, longer length of hospital stay, and poorer quality of life (QoL). [1, 2] Over 100,000 older people undergo such surgery for conditions such as hip fracture [3] and intra-abdominal disorders [4] annually in the UK, and these numbers will increase for the foreseeable future as the number of people aged over 65 years increases. There is little time to optimise anaemia before emergency surgery and the nature of the underlying conditions may make anaemia harder to treat. Newer treatments for anaemia, such as intravenous iron and Erythropoiesis Stimulating Agents (ESA), are being used increasingly in this high-risk group of emergency patients and are postulated to improve outcomes. However, they are costly; the evidence of benefit to patients is lacking, and they may have the potential to cause harm. There are no satisfactory trial data, powered on patient-centred clinical outcomes or on the effectiveness of treatment of anaemia following emergency surgery. [5] [6]

Evidence of burden

Around 70,000 patients undergo surgery for hip fracture [3] and 30,000 emergency laparotomy [4] in the UK every year. The number of people requiring surgery after hip fracture is predicted to rise to over 100,000 per year by 2033 in England alone, costing £3.6–5.6 billion (inflation adjusted) in total care. This is despite improvements in general health and osteoporosis management. [7] At any one time, people with hip fracture occupy the equivalent of 1 in 45 of all hospital beds in England and Northern Ireland, and 1 in 33 hospital beds in Wales. At current rates, hip fracture carries a total cost equivalent of approximately 1% of the total NHS budget. [3]

Anaemia around the time of major emergency surgery is common, affecting 52% of patients before emergency laparotomy; [8] 62% after emergency laparotomy in the UK[9]; and 87% after hip fracture. [10]

Evidence of importance of anaemia

Many small studies have noted an association between anaemia and outcomes. A large observational study of surgical patients having non-cardiac surgery using the American College of Surgeons quality improvement database demonstrated in >227,000 patients that anaemia was independently associated with increased 30-day mortality (odds ratio (OR) 1.42, 95% confidence interval (CI) 1.31 to 1.54) and morbidity (OR 1.35, 95% CI 1.30 to 1.40) after surgery. The effect was present with mild anaemia, but greater with a worse anaemia and when anaemia was present concomitantly with a known preoperative risk factor, increasing the effect of this risk factor on outcomes. [11]

Need for postoperative studies

Most contemporary research into management of anaemia in the surgical population has focussed on optimising patients before surgery using intravenous iron, reducing blood loss at operation or assessing thresholds for blood transfusion. However, these studies fail to address the benefits, risks and costs of treating anaemia after surgery, when pre-operative optimisation is not possible.

There is extensive evidence that liberal use of blood transfusion postoperatively does not improve outcomes; the HTA funded trial RESULT-Hip [12] is investigating transfusion thresholds in people with hip fracture. Regardless of the results of that trial, increasing numbers of patients will be discharged from hospital with anaemia, many of whom remain anaemic as long as 6 months after hospitalisation. [13] Given the association between anaemia

and worse outcomes, and the lack of evidence for transfusion as a treatment, alternative approaches are being sought.

Recent research has focused on pre-operative intravenous iron in elective surgery, aiming to reduce perioperative transfusions, [14-16] which cannot be generalised to emergency surgery, where the focus is on interventions that have to be delivered and tested post-operatively. The recently reported PREVENTT trial [17] of an elective cohort, found no benefit of a single pre-operative dose of intravenous iron in elective surgical patients several weeks before surgery. However, the authors reported an unexpected lower readmission rate at 8 weeks in the intravenous iron group (31/234 (13%) vs 51/234 (22%), OR 0.61, 95% CI 0.40 to 0.91)), supporting the need to look at downstream effects after discharge. In contrast to PREVENTT, other pre-operative intravenous iron studies have shown some improvement in QoL measures, survival and transfusion rates but again in the elective rather than emergency setting. [14, 16]

Evidence for intravenous iron

Stimulating red cell production in the postoperative period is an attractive, biologically plausible approach to improving patient outcomes, and is being used increasingly. [18, 19] A brief review of published literature and key trials is given below.

A previous [20] and updated systematic review and meta-analysis have compared usual care with either intravenous iron or intravenous iron and ESAs to treat patients after hip fracture. The quality of evidence available is poor: only 4 of these studies were RCTs [21-24] and quality of life after surgery was reported as an outcome in only two RCTs. [21, 22] Meta-analysis of the RCTs reported no significant difference in length of hospital stay for the intervention (intravenous iron +/- ESA) (mean difference -0.59 days, 95% CI -1.20 to -0.03, I^2 = 30%, p = 0.23). In the non-randomised studies the sensitivity analysis returned a mean difference in length of stay of −1.07 days (95% CI: −1.85 to −0.28; I^2 = 88%, p < 0.01). Intravenous iron was not associated with a difference in 30-day mortality (n = 732, OR: 1.14, 95% CI: 0.62 to 2.1; I^2 = 0%, p = 0.50), nor with the requirement for transfusion (n = 732, OR: 0.85, 95% CI: 0.63 to 1.14; I^2 = 0%, p < 0.01) in the analysed RCTs. Functional outcomes and quality of life were variably reported in three studies[72].

Systematic review of the use of intravenous iron in emergency surgery to investigate rates of infection and change in haemoglobin [6] identified only three RCTs (two of these were completed in hip fracture). The impact of intravenous iron on recovery and quality of life has not been considered in detail in the emergency laparotomy population, though there are studies relating this to colorectal cancer surgery [14, 16] and major abdominal surgery. [15]

We systematically searched trial registries for ongoing trials in emergency surgery, finding 3 relevant RCTs (NCT03817957, NCT02972294, NCT04083755). Small sample size and mixed populations make definitive, clinically relevant answers for emergency surgery patients highly unlikely. They evaluate transfusion requirement or haemoglobin concentration (Hb) change as primary outcomes, which are largely irrelevant and unmeaningful to patients. We found no RCTs in patients undergoing emergency laparotomy. We identified only two trials of perioperative ESAs, both in the pre-operative setting and both small studies (n=74, NCT03528564 and n=128, NCT04141631). These trials both investigated comparable doses of erythropoietin (EPO) (40,000 IU or 600 IU/kg EPO).

Evidence for erythropoiesis stimulating agents

Erythropoietin is an essential hormone for the production of red blood cells; it is modified and used as a medicinal product in the class of ESAs. Postoperative inflammation, which is common in people after surgery, can lead to decreased production of EPO and also cause

the bone marrow to become resistant to circulating EPO. Elevated hepcidin levels, secondary to inflammation, can also lead to iron 'trapping' in macrophages thereby reducing its availability for erythropoiesis. ESAs such as erythropoietin and darbepoetin, stimulate EPO receptors and reduce hepcidin levels. By providing supplemental iron with the EPO, it may be possible to counteract the iron-restrictive effects of inflammation, as well as the low production and resistance to EPO.

There is good evidence indicating both the efficacy and safety of ESAs in pre-operative surgical patients as well as in critically ill patients. [25, 26] The use of ESAs together with intravenous iron is recommended pre-operatively in several guidelines in order to reduce transfusion rates, and, in particular, in elective orthopaedic surgery [27] [28] and cardiac surgery [29] as well as in patients with renal impairment or patients who refuse blood products. [30] However, the strength of evidence is moderate and effects on clinical outcomes remain unclear. [31] Meta-analyses have shown relative risk of 0.57 (95% CI 0.46 to 0.71) for blood transfusion and numbers needed to treat to reduce any blood transfusion ranging from 3 to 6. [32] [33] The reduction in transfusion rates has been proposed in orthopaedic surgery to be cost-effective if a single dose of EPO 40,000IU costs less than US $225. [34] [35] Whether a reduction in transfusion rates translates to a change in outcomes such as days at home is yet to be determined, but in a Cochrane Review of cancer patients there is suggestive evidence towards benefits in QoL. [36]

Our trial has been designed specifically to address the impact of these two widely used interventions simultaneously. Intravenous iron appears to reduce the dose of ESA required to increase haemoglobin pre-operatively and is superior to the combination of ESA and oral iron. [37] [38] This enables the pragmatic choice in this trial for a single postoperative dose of an ESA and this is current practice in other counties (personal communications, unpublished data Prof Spahn (Switzerland) and Prof Munoz (Spain)). In the meta-analysis by Kei *et al.*, [32] ESAs and intravenous iron together were superior to intravenous iron alone for reducing blood transfusions. This all supports a synergistic effect that requires exploration.

Potential non-haemoglobin related benefits of iron and ESAs

Intravenous iron and ESAs may have additional benefits beyond increasing haemoglobin. Iron is needed for haemoglobin synthesis in red cells, which is essential for adequate oxygen delivery. [39] It is part of myoglobin in muscles and a component of many metabolic processes required for DNA synthesis and neurotransmission. [39] Low iron status, even in the absence of anaemia, has been linked to cognitive dysfunction, impaired immunity, reduced exercise capacity, cardiopulmonary dysfunction and adverse maternal outcomes. [39-42] Intravenous iron has been shown to have beneficial effects on oxygen consumption, exercise capacity, and cardiopulmonary function independent of anaemia. ESAs have been shown to decrease mortality in critically ill patients and this may be mediated through anti-inflammatory and anti-apoptotic pathways that target a common pathway of inflammation. [43] ESAs have been shown to improve muscle function after hip fracture, a key determinant of postoperative functional recovery. All these effects are relevant to recovery after major surgery and warrant further investigation.

Potential safety concerns - risk of infection and thrombosis

Iron and ESAs are commonly used safe drugs, but the risks of infection with intravenous iron, [26] and thrombosis with ESAs, [44] [45] remain unclear and both may be exacerbated if there is acute inflammation. In our review of all RCTs, intravenous iron was associated with increased risk of infection when compared with oral iron or placebo (risk ratio [RR] 1.17, 95% CI 1.04 to 1.31) in 64 trials (N=19,480). [46] We also found that there was considerable variation in the reporting of infection in included RCTs. Only ten RCTs used a standardised

(or established) definition of infection which may limit our understanding of the true nature and extent of this risk.

Regarding EPO, one meta-analysis reports an increase in thrombotic risk in spinal surgical patients not receiving thromboprophylaxis, [33] and another did not find an increased risk for mortality or thrombotic-related events. [32] A recent meta-analysis in critically ill patients found no evidence of an effect of EPO on thrombotic complications (RR: 1.17, 95% CI 0.87 to 1.58, 12 trials, N = 3,759). [44] In a Cochrane review looking at the effects of EPO and darbepoetin in cancer patients, the authors found a reduction in blood transfusions (RR 0.65; 95% CI 0.62 to 0.68, 70 trials, N = 16,093) but an increase in risk of thromboembolic complications and all-cause mortality (RR 1.52, 95% CI 1.34 to 1.74, 51 trials, N = 15,498). There was also suggestive evidence towards an increased QoL and insufficient evidence towards an effect on tumour progression. [36] How these findings extrapolate to cancer patients having emergency surgery is unclear.

The adverse effects of one single dose, as proposed in this trial, rather than multiple doses also need to be considered. Multiple doses exceeding 80,000 IU of EPO may be more effective and harmful than a single dose under 80,000 IU. [32] Similarly, adverse effects are seen more commonly with haemoglobin (Hb) values above 110g/l (our trial targets patients with Hb values of 80–110g/l) or with rapid rises in Hb. We will exclude patients with absolute contraindications to ESAs such as uncontrolled hypertension, thrombocytosis, red cell aplasia and active thrombo-embolic disease.

Why is this research needed now?
There is an urgent need to determine whether the poor outcomes associated with postoperative anaemia in older patients can be reduced. Over 100,000 patients already undergo emergency surgery every year and this is projected to increase with the ageing population. The personal and societal costs of trauma are immense, and even small benefits are worthwhile. Despite the absence of high-quality evidence, data [47] [48] show that interventions such as intravenous iron continue to be used in these patient groups. National guidelines and consensus statements are driving changes in practice in this field of medicine.

The role of these drugs has not yet been ascertained and, importantly, neither have the risks associated with using these agents to treat older, post-emergency surgery patients. From an economic perspective the cost of the drugs is significant, and a full assessment of the benefits and undesirable effects of the drugs is warranted to support / refute the use of this resource. Treatment with intravenous iron and/or ESA will be costly if used for large numbers of patients but may not be either clinically or cost-effective.

Time spent at home is valued by patients, even over survival. Reducing length of stay, readmissions and the need for care outside the home are all realistic goals, resulting in more days at home. Patients view the ability to function similarly to before surgery as particularly important. No previous clinical trials have been adequately powered on patient-centred outcomes – a definitive trial is required to address this important clinical issue.

4. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Description

There will be two active treatments evaluated in the trial.

- **Ferric derisomaltose (i.e. Iron)**

Active ingredient: Ferric derisomaltose (defined by active substance only)
Dosage form: 100 mg iron/ml for injection/infusion
Appearance: Dark brown, non-transparent aqueous solution
Excipients: Sodium hydroxide, hydrochloric acid, water for injection

- **Darbepoetin alfa (i.e. ESA)**

Active ingredient: Darbepoetin alfa (defined by active substance only)
Dosage form: Dose range 10–500 mcg/ml for injection in pre-filled syringes
Appearance: Clear, colourless solution
Excipients: Sodium phosphate monobasic and dibasic, sodium chloride, polysorbate 80, water for injection
Strength/packaging: Solution for injection in pre-filled syringe (Range 25–500 mcg/ml); Solution for injection in pre-filled pen (SureClick) (Range 25–500 mcg/ml)

Manufacture

The IMPs for the trial are defined by their active substance and dosage only. Sites are permitted to use product provided by any known manufacturer provided the use of the product in this trial falls within their marketing authorisation.

Example manufacturers:

- **Ferric derisomaltose**

Manufacturer: Pharmacosmos, Reading, UK
Marketing authorisation number: PL 18380/001

- **Darbepoetin alfa**

Manufacturer: Amgen Ltd, Cambridge, UK
Marketing authorisation number: PLGB 13832/0075

Packaging and labelling

In accordance with the Medicines and Healthcare products Regulatory Agency (MHRA) risk-adapted approach to the management of clinical trials of investigational medicinal products, and the pragmatic nature of the trial, this trial will not require trial specific packaging or labelling. All treatments being used in this trial are established treatments with well documented safety profiles. Treatments will be prescribed and dispensed from routine stocks and are widely prescribed in secondary care.

The local pharmacy will be responsible for sourcing the IMPs. An authorised and appropriately trained member of the site research team will be responsible for preparation and administration of the IMP according to the SmPC or relevant local procedures.

Upon randomisation by an authorised member of the site research team, a confirmation of randomisation will be generated within the trial database, containing the participant's trial identification number, initials and date of birth along with details of the allocated treatment.

The confirmation of randomisation will be filed (or scanned) in the participant's medical record as evidence that the treatment has been prescribed for the purposes of a clinical trial.

Storage, dispensing and return

There are no trial-specific requirements for the storage, dispensing or return of any of the IMPs used in this trial. All treatment prescribed and dispensed for the purpose of the trial will originate from standard clinic stock. It is the responsibility of the local hospital pharmacy to ensure that drugs are stored in accordance with the manufacturer's storage instructions as detailed in the applicable Summary of Product Characteristics (SmPC). Sites will follow their own local policies for the documentation of storage and dispensing at pharmacy and ward level.

Placebo

There is no placebo in this trial. The comparator group receives usual care.

Known Side Effects

Table 1: Known side effects for ferric derisomaltose - the below information has been taken from section 4.8 of the SmPC (see Reference Safety Information below):

MedDRA system organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known
Immune system disorders		Hypersensitivity, including severe reactions	Anaphylactoid/ anaphylactic reactions	
Nervous system disorders		Headache, paraesthesia, dysgeusia, blurred vision, loss of consciousness, dizziness, fatigue	Dysphonia, seizure, tremor, altered mental status	
Cardiac disorders		Tachycardia	Arrhythmia	Kounis syndrome
Vascular disorders		Hypotension, hypertension		
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea, bronchospasm		
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, dyspepsia, constipation, diarrhoea		
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria, flushing, sweating, dermatitis	Angioedema	Distant skin discolouration
Metabolism and nutritional disorders		Hypophosphataemia		

Musculoskeletal and connective tissue disorders		Back pain, myalgia, arthralgia, muscle spasms		
General disorders and administration site conditions	Injection site reactions*	Pyrexia, chills/shivering, infection, local phlebitic reaction, skin exfoliation	Malaise, influenza like illness**	
Investigations		Hepatic enzyme increased		

Table 2: Known side effects for darbepoetin alfa - the below information has been taken from section 4.8 of the SmPC (see Reference Safety Information below):

MedDRA system organ class	Very common (>1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not known
Immune system disorders	Hypersensitivity			Serious allergic reaction incl. anaphylaxis, angioedema, allergic bronchospasm and urticaria.
Nervous System Disorders			Convulsions	
Cardiac disorders		Hypertension		
Vascular disorders		Thrombosis		
Skin and Subcutaneous disorders		Rash/erythema		SJS/TEN, multiforme, blistering, skin exfoliation.
General disorders and administration site conditions		Oedema		
		Injection site pain	Injection site bruising or haemorrhage	

Reference Safety Information:

The Reference Safety Information (RSI) will be section 4.8 of the SmPCs described in the documents listed below:

Ferric derisomaltose: Monofer 100 mg/ml solution for injection/infusion (15 August 2022)

Darbepoetin: Aranesp solution for injection in pre-filled syringe (06 April 2022)

5. TRIAL OBJECTIVES AND PURPOSE

Purpose

The purpose of the trial is to investigate, in patients 60 years or older recovering from major emergency surgery, whether treating postoperative anaemia with intravenous iron, or intravenous iron plus ESA, is clinically beneficial and cost-effective when compared with usual care, from the patients' perspective.

This will allow us to provide robust, evidence-based guidance on the use of these drugs within urgent/emergency surgery clinical pathways.

If either the iron monotherapy or iron combined with ESA combination therapy demonstrates benefit, we anticipate rapid adoption across the NHS, providing direct QoL improvements in older people (and indirectly potentially to their families and/or carers) following emergency surgery.

The benefits may be partially attributable to reductions in length of acute stay / readmissions to hospital. We have estimated that the costs of current length of stay for hip fracture patients and intra-abdominal disorder patients to be £8,295 and £8,848 respectively. With an estimated 100,000 patients annually receiving treatment for hip fractures or intra-abdominal disorder the total bed costs over £846M annually – a reduction in these costs will directly benefit the healthcare system.

Conversely, if the trial demonstrates no benefit or clinical cost-ineffectiveness, then we anticipate prompt guidance to stop the use of intravenous iron in the postoperative period. If the trial demonstrates this there could be a large cost-saving to the NHS, and a reduction in treatment burden for patients.

The research will also provide useful data for future research on distributions of outcomes following emergency surgery in an older population. In particular, the functional and QoL outcomes that are currently sparsely reported.

PRIMARY OBJECTIVE

To assess the clinical effectiveness of postoperative intravenous iron and intravenous iron plus a subcutaneous injection of an Erythropoiesis Stimulating Agent (ESA) compared to a usual care control group respectively, for the treatment of anaemia across two major patient groups who have had emergency surgery.

SECONDARY OBJECTIVES

1. To monitor safety of the interventions.

2. To conduct an internal pilot to evaluate recruitment, uptake and retention rates, sample size parameter estimates, clinician protocol adherence, safety, adherence to treatment allocation, completeness, and quality of data collection.

3. To assess the cost effectiveness/cost utility of postoperative intravenous iron and intravenous iron plus ESA compared to a usual care control group respectively, and

impact on resource use and quality of life from a healthcare, social care and broader societal viewpoint.

6. TRIAL DESIGN

TRIAL CONFIGURATION

Design: Multi-site, multi-arm, open-label pragmatic randomised controlled trial with internal pilot and concurrent economic evaluation. The trial is predicated on two primary comparisons of a monotherapy and a combination therapy each individually compared with a single common usual care control group respectively, in a superiority hypothesis testing framework.

Trial setting: Approximately forty acute hospitals providing care to people with hip fracture or requiring emergency laparotomy in the UK.

Primary endpoint

- **Days at home at 30 (DAH30)**

Reported by participants or their Personal Legal Representative (PLR), or other person with close knowledge of the participant (e.g. staff from a nursing home), DAH30 is an integer between 0 and 30 that reflects, out of the 30 days following randomisation, the total number of those days that the participant spends alive and at home ('home' being defined as the place of 'usual residence', which can include residency in a care home or assisted living, etc). DAH30 is derived by subtracting from 30 the duration of initial length of stay following randomisation, as well as the duration of any further readmissions (to hospital or elsewhere) in the first 30 days. All days spent not at home, other than holidays, are also subtracted. These include moving house to more dependent living, time spent with relatives, etc. If a participant never returns home or dies at any point within the first 30 days, they will be assigned a score of 0.

Days at Home at 120 days, a secondary endpoint, is calculated in the same way but within 120 days since randomisation.

Secondary endpoints

- **EQ-5D-5L**

Reported by participants or their Personal Legal Representative (PLR), or other person with close knowledge of the participant (e.g. staff from a nursing home), the EuroQol-5 Dimension-5 Level (EQ-5D-5L)[76] health status measure is a widely used generic instrument for describing and valuing health states.

- **NHFD Residential Status**

Obtained from medical records at discharge. Categorised using the same ordinal scale as used by the NHFD: (1) own home/sheltered housing, (2) residential care, (3) nursing care, (4) rehabilitation unit – hospital bed in the current trust, (5) rehabilitation unit – hospital bed in another trust, (6) rehabilitation unit – NHS funded care home bed, and (7) acute hospital.

- **Walking Performance**

Reported by participants or their Personal Legal Representative (PLR), or other person with close knowledge of the participant (e.g. staff from a nursing home), using the 'New Mobility Score', which has been utilised by the National Hip Fracture Database (NHFD)[73].

- **Length of Stay**

Obtained from medical records, the length of stay is an integer that describes the number of days a patient was in hospital following randomisation. Calculated by obtaining the date of discharge from hospital records and then counting the number of nights between this date and the date of randomisation.

- **Complications**

Medical records for all patients will be reviewed by appropriately trained staff for indicators of infection at the time of the patient's discharge from the recruiting site. In addition, for those patients who have left hospital, the patients will self-report (via an online form, telephone interview or by post, at 30 and 120 days after randomisation) on any of the complications listed below. For those patients lacking capacity, their PLR/ will be asked to provide this information.

Participants will be asked about the following complications:

Related systemic complications:

- Chest infection/pneumonia
- Urinary tract infection
- Other source of systemic infection
- Cerebrovascular accident
- Myocardial infarction/acute coronary syndrome
- Blood transfusion
- Acute kidney injury
- Pulmonary embolism
- Deep vein thrombosis

Related local complications:

- Wound infection (deep as defined by CDC criteria*)
- Additional surgery related to hip fracture/emergency laparotomy (including intra-operative)

*Deep surgical site infection (SSI) is defined by the Centres for Disease Control and Prevention as a wound infection involving the tissues deep to the skin [68].Upon indication of potential signs of infection at 120 days by the patient or PLR/, the research team at the recruitment site and/or General Practitioner will be asked to review the patient's medical records to confirm the diagnosis of deep SSI.

- **Hospital Resource/Cost Data**

Obtained from hospital records, this measure defines the resources and cost associated with a patient's hospital episode.

- **Days alive and out of hospital**

Obtained from hospital records, 'Days alive and out of hospital' **(**DAOH30) is an integer between 0 and 30 which reflects, out of the 30 days following randomisation, the total number of those days that the participant spends alive and out of hospital. It is computed using Hospital Episode Statistics – Admitted Patient Care (HES-APC) which captures date of discharge and readmissions within 30 days.

- **Health Resource Use Questionnaire – Post intervention costs healthcare/ social and societal**

Reported by participants or their Personal Legal Representative (PLR), or other person with close knowledge of the participant (e.g. staff from a nursing home), this is a purposely designed proforma to capture health and social care costs as well as costs from a societal and patient perspective (such as employment).

- **Mortality**

Obtained from hospital records, or through linkage with NHS central records, mortality is a binary outcome that defines whether a patient has died between day 0 (randomisation) until day 120.

Safety endpoints

- Adverse reactions to treatment drugs: ferric derisomaltose and/or darbepoetin alfa.
- Serious adverse events.

Stopping rules and discontinuation

There are no planned formal interim analyses. The Sponsor reserves the right to discontinue this trial (in part or whole) at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee (TSC), Data Monitoring Committee (DMC) and the funder (National Institute for Health Research Health Technology Assessment - NIHR HTA) before making this decision.

An internal pilot has been built into the trial to allow a feasibility assessment which will examine recruitment, retention, and adherence. These progression criteria, outlined below, will be continuously monitored and a formal review will take place 10 months after the first participant is randomised into the trial.

Table 4: Internal pilot progression criteria

	Red	Amber	Green
Threshold (%)	50–74%	75–99%	100%
Total number of sites open	<30	30–39	40
Total number of patients randomised	<400	400–543	544
Retention at 30 days i.e., primary outcome ascertainment (of those able to have complete data at 10-month pilot review)	<75%	75–94%	95%
Adherence to intervention	<75%	75–94%	95%
Action	Urgent discussions with TSC & HTA regarding remedial measures	Continue, with recovery plan tba with TSC and HTA	Continue, no action needed

RANDOMISATION AND BLINDING

Randomisation

Following screening and participant identification, informed consent and collection of baseline data, eligible participants will be randomised (allocation ratio 1:1:1) to receive either usual care, usual care plus intravenous iron monotherapy, or usual care plus combination intravenous iron and a subcutaneous injection of ESA. Allocation will be concealed using a web-based randomisation system developed and maintained by the Nottingham Clinical Trials Unit (NCTU) and hosted on a secure server, accessed via a password-protected 24/7 secure website.

Participants will be randomised with equal probability using a probabilistic minimisation algorithm balancing across the three groups on five important factors:

- Recruiting site
- Type of surgery (emergency laparotomy or hip fracture)
- Age group at randomisation (60–74/75–79/80–84/85–89/90+)
- Sex (male or female)
- Postoperative haemoglobin concentration at randomisation (<100 g/l or ≥100 g/l)

Upon randomisation by an authorised member of the research team, a confirmation of randomisation will be generated within the trial database, containing the participant's trial identification number, initials and date of birth along with details of the allocated treatment. The confirmation of randomisation will be filed (or scanned) in the participant's medical record.

Blinding

Blinding of trial participants, researchers and clinicians is impractical due to the differing nature of the drug preparations, mode of administration and frailty of the participants. Therefore, there will be no placebo medications.

Table 5: Blinding Status of Trial Staff

Group	Blinding status
Participants	Not blinded
Researcher (prescribing the intervention)	Not blinded
Researcher (collecting in hospital data)	Not blinded
Researcher (collecting follow up data)	Not blinded
Chief Investigator	Blinded
POP-I Trial Management	Not blinded
Trial Statistician	Blinded[1]
Trial Health Economist	Blinded[1]
Independent Statistician	Not blinded
Data Monitoring Committee	At their discretion

[1]The trial statisticians and trial health economists will be blinded to treatment allocation prior to the final analysis.

Access to group assignment will be restricted to a member of NCTU not otherwise involved in the trial and will be stored securely.

Maintenance of randomisation codes and procedures for breaking code

As participants and drug administrators are not blinded to treatment allocation, there is no process required for code breaking. PIs and clinical staff will, in the event of emergency, be able to identify treatment allocation from the participant's medical record.

At their request, the Data Monitoring Committee (DMC) may review unblinded data. This will be prepared by a statistician from NCTU not involved in the trial (i.e., an independent statistician).

Treatment allocations will be identified by reference to the master randomisation log once data analysis (blinded) is complete.

TRIAL MANAGEMENT

The TSC will typically meet at least once a year (or as required) and will provide independent oversight of the trial on behalf of the trial sponsor. The DMC will typically meet at least once a year (or as required) to assess effectiveness and safety and will report to the TSC. The Trial Management Group (TMG) will meet more frequently, typically once per month, and will be responsible for the day-to-day management of the trial.

All the oversight groups will have terms of reference/charters agreed in advance of participant recruitment.

The Chief Investigator has overall responsibility for the trial and shall oversee all trial management. The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

Participant Duration:
Patients will be approached between day 1 and day 10 after emergency surgical operation. Entry to the trial and randomisation will occur within this period. The duration of follow-up after this entry point is 120 days.

Trial Duration:

The trial will take place over 4 years.

End of the Trial

The end of trial will be the final database lock. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Should the trial be terminated early, NCTU will inform the MHRA and REC within 15 days of the end of trial. NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Screening and Recruitment

The trial will take place in UK hospitals providing emergency care to patients requiring surgical management of hip fracture and/or emergency laparotomy. Participants will be recruited from hospital wards and critical/enhanced care areas.

Patients aged 60 or over who have undergone either emergency hip fracture surgery (as defined by National Hip Fracture Database (NHFD)) or emergency laparotomy (as defined by National Emergency Laparotomy Audit (NELA)) will be identified after surgery from theatre lists, admissions lists and ward patient records. Potential participants may also be identified through daily 'board rounds' and 'trauma meetings' on wards. The initial approach will be from a member of the patient's usual care team (which may include the PI), and information about the trial may be on display in the relevant clinical areas (at each individual site's discretion).

The routine blood tests of these patients will be monitored to determine if they develop post-operative anaemia (i.e. Hb 80-110 g/L). If a patient is deemed eligible on these criteria, then patients may be approached to discuss the trial at any point between day 1 and day 10 post-surgery, and before discharge from hospital. If patients are initially too unwell or suffering infective complications then recruitment to the trial may be delayed until the patient has recovered, and the patient can be recruited later within the day 1 to day 10 post-operative recruitment window.

It is anticipated that some of the population included in this trial, and in particular a significant proportion of patients presenting to hospital with hip fracture, will not have capacity to consent to the trial. For these patients, consent may be given by a personal legal representative (PLR).

If a patient meets the inclusion criteria then the patient or their PLR/ will be given a participant or PLR/ information sheet, and the local researcher/delegated staff will explain the trial. The PI (or delegate) will inform the participant or their PLR/, of all aspects pertaining to participation in the trial. Sufficient time will be given for the patient to consider participation, a minimum of 30 minutes. The patient will be given the opportunity to ask questions throughout the process. The PI (or delegate) will obtain consent as authorised and documented on the Site Delegation Log. It remains the responsibility of the PI to ensure informed consent is obtained appropriately and that those on the delegation log have been appropriately trained.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial. Consent forms and information sheets will be available in four other languages: Welsh (as an official UK language), and Polish, Romanian and Panjabi as the three

most common non-English/Welsh languages spoken in the UK. Translation of documents will be undertaken by third-party professional translation services.

It will be explained to the potential participant (or their PLR/,) that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

A screening log will be maintained at each trial site within the trial database detailing potential participants and reasons for not entering the trial. This will be used to inform the internal pilot phase and to guide and inform the recruitment process.

Patients on the screening log who do not meet the inclusion criteria due to the haemoglobin level being outside of the target range should continue to be screened using routine blood tests performed for usual clinical care. If the patient then triggers inclusion in the trial by meeting the haemoglobin target range (80–110 g/L) they may then be recruited to the trial if they are within the day 1 to day 10 post-surgery window and meet all other criteria.

Eligibility criteria

Inclusion criteria

- Age 60 years or older
- Hb 80–110g/l measured on any day between day 1 and day 10 after surgery.
- Major non-elective surgery in the last 1 to 10 days: Patient will have undergone either Emergency Laparotomy as defined by National Emergency Laparotomy Audit (NELA) ***OR*** Fragility Hip Fracture surgery as defined by National Hip Fracture Database (NHFD).
- Written informed consent from participant or PLR.

Exclusion criteria

- Use of intravenous iron, darbepoetin or other ESAs in last 30 days.
- Haematological diagnoses where iron overload is a risk (e.g., haemochromatosis or alpha-thalassaemia trait) or alternative treatments are indicated (e.g., haematological malignancies).
- Acute uncontrolled infection as judged by the treating clinician (e.g. ongoing bacteraemia or non-resolving sepsis) or patient expected to be on non-prophylactic antibiotics for greater than 14 days.
- Contraindication to thromboprophylaxis.
- Direct contraindications to IMP:
    - disturbances of iron, iron overload
    - thrombocytosis
    - uncontrolled hypertension
    - red cell aplasia
    - active thrombo-embolic disease
    - decompensated / severe chronic liver disease (Child Pugh C)
    - advanced cancer (metastatic and/or receiving chemo/radiotherapy)

- Patient not expected to survive for 30 days
- Renal replacement therapy
- Immunosuppressive therapy for organ transplant

Other notes on exclusion criteria

- Oral iron prescribed and administered before admission is not an exclusion criterion. However, oral iron administered after randomisation is a prohibited concomitant treatment (see concomitant treatments).

Expected duration of participant participation

Participants will be involved in the trial for 120 days. Active participation will cease after a participant completes the final set of questionnaires on day 120 or as soon as possible thereafter.

Co-enrolments

There is a chance that patients may be approached for participation who are already enrolled in a trial elsewhere. Our experience (and that reported in the literature) is that this can be conducted appropriately and sensitively, and that patients and research teams in this situation are capable of making an informed decision about whether participation is appropriate. The Chief Investigator will discuss with both Sponsors and agree whether co-enrolment is acceptable and agreed by separate contracts with each site.

Removal of participants from therapy or assessments

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

If a participant requests to withdraw from the trial, it may be possible for them to reduce their involvement in trial activities without completely withdrawing from the study (i.e. discontinuation rather than withdrawal). This may aid in the collection of the primary outcome measure. The NCTU must be informed of all requests to discontinue research activities from participants.

Participants may discontinue one or all of the following activities:

Table 6: Discontinuation of Participant Involvement

Discontinuation type	Discontinuation procedure	Use of data that are already collected
Discontinue from receiving IMP administration.	Participants only receive the IMP once, shortly after providing consent and baseline measures. Participants who discontinue from treatment administration will remain in the trial and their data will be collected as per protocol,	N/A discontinue from treatment only

	unless they explicitly state otherwise.	
Discontinue from follow-up questionnaires at day 30 and day 120.	Should a participant request to be removed from questionnaire follow-up, they will be asked for verbal consent to receive a short telephone call at 30 days post-randomisation to answer the primary outcome measure (i.e. DAH30 – a one item measure). This verbal consent will be clearly documented in the trial database in a 'Discontinuation Form'. Should participants refuse this short form follow-up they will be marked as 'Full Trial Withdrawal' (see below).	Any data collected prior to request (i.e. data obtained at baseline) will be retained and used.
Discontinue from other trial communications.	Any patient who requests to be withdrawn from other trial communications will be removed from all mailing lists for ongoing trial contact (e.g. newsletters and reminders) but will still receive trial questionnaires.	N/A discontinue from communications only
Full trial withdrawal	Any participant that requests to have no further involvement in the trial will be marked as withdrawn on the trial database.	Any data collected prior to participant withdrawal will be retained and used.

Withdrawn participants will not be replaced. The sample size has allowed for up to 5% non-collection of primary outcome data.

Informed consent

Patients who are eligible and deemed by the clinical or research team as able to give consent for themselves will be asked to provide written informed consent. It is anticipated that some of the population included in this trial, and in particular a significant proportion of patients presenting to hospital with hip fracture, will not have capacity to consent to the trial. These patients may be consented by a PLR.

Consent for participants with capacity

All participants with capacity will provide written informed consent (in either a paper format, or through e-consent, see below). The Informed Consent Form (ICF) will be signed and dated by the participant before they enter the trial. The PI (or delegate) will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not (a minimum of 30 minutes). The PI will answer any questions that the participant has concerning trial participation. The researcher will ensure that they

adequately explain the aim, trial treatment, potential benefits and potential hazards of taking part in the trial to the potential participant. The researcher will also emphasise that participation is voluntary and so the potential participant is free to decline participation and may withdraw from the trial at any time.

Informed consent will be received from each participant before they undergo any interventions related to the trial. A medical doctor will always confirm eligibility for the trial.

Witnessed Consent

Patients who are eligible and are deemed to have the capacity to consent, but who cannot sign a consent form (e.g. due to significant sight loss or dexterity issues) may give verbal consent to the trial to the PI or delegate. This will be recorded on the 'witness consent' section of the participant consent form by a member of the research team. This consent will be witnessed by an independent witness who will countersign the consent form.

Consent for participants without capacity

Some participants may not be able to give consent due to pre-existing dementia or other forms of cognitive dysfunction (e.g. post-operative delirium). Investigators and other research team members involved in the enrolment of trial participants are responsible for assessing decision-making capacity in accordance with UK law. For some participants this may be a temporary state that improves after surgical treatment and care; for others it will be more chronic or permanent. We believe that it is important to include all patients, including those with temporary or permanent incapacity to consent, in this trial to maintain its relevance and generalisability to the population being studied. Patients without capacity will be recruited to the trial in line with the clinical trials regulations.

If a patient is deemed not have capacity to consent then a personal legal representative (PLR) will be approached to provide consent on the patient's behalf. The PLR will typically be a family member or person with lasting power of attorney. The PLR will be provided with a PLR Information Sheet and the PI or delegate will explain the details of the trial. The PLR will have time to consider participation on the patient's behalf (a minimum of 30 minutes) and have the opportunity to ask questions. Written informed consent (either on paper or by e-consent) will then be collected from the PLR before the participant can undergo any interventions related to the trial.

If a PLR provides consent for a participant to take part in the trial but does not have regular contact with the participant (e.g. a daughter who lives in a different part of the UK) then they will be unable to provide follow up information at day 30 and day 120. In these instances, we will contact another person with close knowledge of the participant (e.g. staff from a nursing home) to attempt to collect follow up data at day 30 or 120. This process is clarified in the PLR ICF. It may not be possible to gain responses for every outcome measure at day 30 and 120, but attempts will be made to collect the primary outcome measure (i.e. DAH30) as a bare minimum.

Should a participant regain capacity prior to hospital discharge, the PI or delegate will discuss the trial with the participant and complete a participant ICF for the ongoing trial participation. The PI or delegate will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the potential participant. The PI or delegate will also emphasise that continued participation is voluntary and the participant is free to withdraw from the trial should they wish. This discussion will be clearly documented in the participant's medical records and the trial database.

Electronic consent (e-consent)

Sites can choose to receive consent on paper or by e-consent (i.e. collected electronically via the trial database). This may be in circumstances where a PLR wishes to provide consent on

behalf of a participant, but they are unable to physically attend the hospital to sign a paper consent form.

If e-consent is being used in-person (e.g. on the ward) then the PI or delegate is required to talk the participant/PLR through each point on the ICF that is presented on an internet enabled device (e.g. a tablet). The participant/PLR must then initial each statement to indicate they are giving fully informed consent for each element of the ICF. The ICF is then signed electronically by the participant/PLR and countersigned electronically by the PI or delegate. Electronic signatures take the form of a traced signature on a touch screen device. A copy of the fully signed ICF is then sent automatically to the participant/PLR and the trial site by email. A copy will be printed for filing in the participant's medical notes and another copy filed in the ISF.

If e-consent is being used remotely (e.g. for a PLR who cannot attend the hospital) then the PIS and ICF will be sent electronically (by SMS or email) via a hyperlink. After the PLR has had the opportunity to read and consider the trial, the PI or delegate is required to talk the participant/PLR through each point on the ICF over the telephone. The PLR must then tick a box against each statement to indicate they are giving fully informed consent for each element of the ICF. The ICF is then signed electronically by the PLR and is sent back to the research site. This document is then downloaded, printed and countersigned (wet ink) by the PI or delegate. Electronic signatures take the form of a traced signature on a touch screen device. A copy of the fully signed ICF is then sent to the participant/PLR and the trial site by email. A copy will be printed for filing in the participant's medical notes and another copy filed in the ISF.

Documenting consent

Once the participant is entered into the trial, the participant's unique trial identification number will be entered on the ICF that is kept in the Investigator Site File (ISF). One copy of the ICF will be given to the participant (or PLR), one copy will be filed in the medical notes, one copy will be electronically uploaded to the trial database for central monitoring by NCTU, and the original will be placed in the ISF.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, version number of ICF signed and the date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note will be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form, which will be signed by the participant.

7. TRIAL TREATMENTS AND REGIMEN

Trial Outline

Baseline

After consent is recorded to take part in the trial, the participant will be randomised to one of the three trial groups. At this point, baseline bloods will be taken/recorded (routine bloods will be used where available) and the following blood tests will be requested: Full blood count, LFT, CRP, Ferritin, Tsat and Transferrin. Next, baseline characteristics will be recorded, the Health Resource Use Questionnaire and the EQ-5D-5L will be administered. Participants will be asked to complete the EQ-5D-5L to indicate their current health (i.e. whilst still in hospital post-surgery) *and* their health two weeks prior to hospital admission. *If* an active intervention

is allocated, then the intervention will be administered as soon as feasible (ideally on the same day as randomisation, but crucially before discharge from hospital).

Adverse events/serious adverse events
Adverse events will be reported until day 7 or discharge, whichever comes first.

Discharge
Length of stay, residential status, complications and hospital resource/cost data will be recorded on the day of discharge by the research team. Prior to discharge, participants will be given a POP-I trial postcard as a reminder of the trial follow-up schedule.

Follow-up
Prior to any follow-up activities during the trial, researchers will check the mortality status of participants before sending out any information. Follow up at 30 days and 120 days after randomisation will primarily be conducted online (by sending participants hyperlinks to questionnaires), but participants can choose to receive follow up by telephone or post. Outstanding questionnaires not received back from participants will be followed up by a member of the research team via email, SMS, post or telephone. Questionnaires may be completed via these methods (e.g. over the telephone) where necessary to increase data completeness. Please see the '*Assessment, data collection, and intervention schedule'* table below for details of the measures administered at day 30 and day 120.

For those participants who lacked capacity to consent at enrolment and at discharge, their data is collected from either the PLR or, where the participant does not live or have regular contact with the PLRby a professional who cares for the participant in some way (e.g. day carer, nursing home staff, GP). This will be decided on a case-by-case basis. It may be that the professional approached is not able to answer the outcome measures relating to Quality of Life. In these cases, the POM (i.e. DAH30) will be recorded as a minimum. If a participant lacked capacity to consent at enrolment but regained capacity prior to discharge, then the participant (after providing consent to continue participation) will provide the data for the follow up measures.

Trial Flow Chart

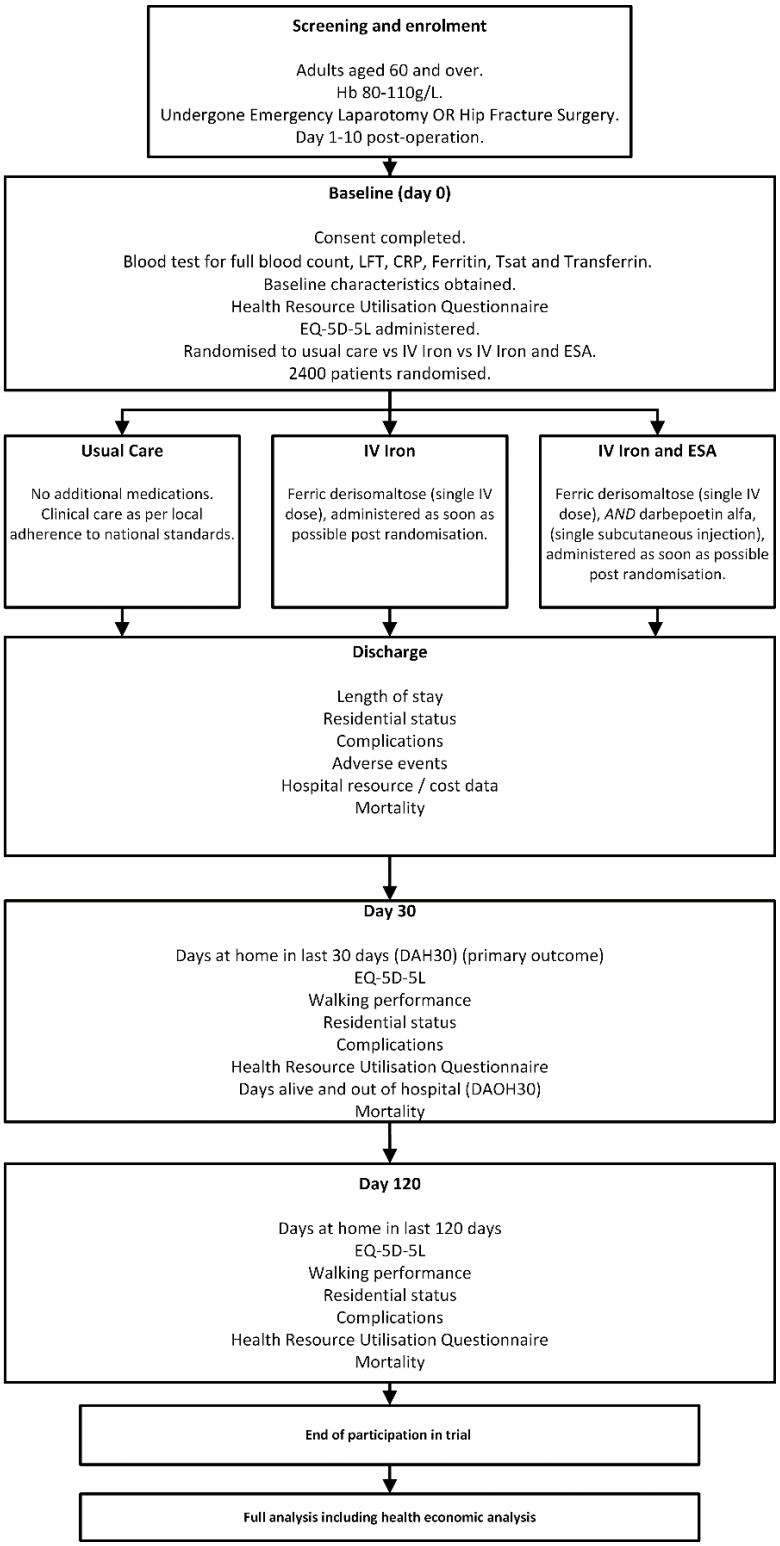

Table 3: Assessment, data collection, and intervention schedule

	Eligibility	Baseline	Discharge	Day 30	Day 120
Full blood count	Bloods				
Full blood count, LFT, CRP, Ferritin, Tsat and Transferrin		Bloods			
PIS/Consent		Person			
Baseline characteristics		Person/Notes			
EQ-5D-5L (QoL)		Person		FU	FU
IMP administration		Person			
Walking performance				FU	FU
Residential status				FU	FU
Length of stay			Notes		
Complications			Notes	FU	FU
Adverse events/serious adverse events*			Notes		
Hospital resource / cost data			Notes		
DAH30 / DAH120				FU	FU
Days alive and out of hospital (DAOH30)				Notes	
Health Resource use Questionnaire		Person		FU	FU
Mortality			Notes	NHS Spine	NHS Spine

Person: In person, on the ward.
Bloods: Blood test.
Notes: Review of relevant records.
FU: Follow-up process (as detailed above, combination of SMS, email, post, telephone).
**Discharge or day 7, whichever comes first.*

USUAL CARE

All sites will provide care aligned to national standards and guidelines for all three groups including: NICE CG124, NHFD, Association of Anaesthetists (hip fracture); NELA (emergency laparotomy); Best Practice Tariff (emergency laparotomy and hip fracture).

Some patients may receive a blood transfusion during the trial period. We recommend following national guidelines for transfusion policies outlined in the table below. Blood transfusion is a scarce resource, associated with risks. These thresholds and targets will not affect our inclusion criteria.

Table 7: Usual Care Guidelines

Guideline	Transfusion trigger/threshold	Target haemoglobin
NICE 2015		
Use restrictive transfusion threshold in patients who do not have major haemorrhage, acute coronary syndrome or who need regular transfusions for chronic anaemia.	70 g/L	70–90 g/L
Acute coronary syndrome	80 g/L	80–100 g/L
Association of Anaesthetists 2020 (Hip fracture)		
Younger, fitter patients		70–80 g/L
Frail patients		>90 g/L
History of ischaemic heart disease or who fail to mobilise on the first day due to fatigue or dizziness		>100 g/L

The IMPs in the iron monotherapy and iron plus ESA combination therapy groups will be administered by a member of clinical staff who is delegated the task of IMP administration in the 'Delegation of Responsibilities Log' at each site. In all cases the IMPs will have been added to the patient's medication chart, authorised and safety checked by another competent clinical colleague (as is routine with all drug administrations). As the IMP will be administered in the hospital setting there will always be appropriate resuscitation facilities and other clinical staff available in the event of an emergency.

IRON MONOTHERAPY: Usual care plus a single dose of intravenous ferric derisomaltose (approximately 20 mg/kg) administered before hospital discharge. The drug dosage is outlined in the SmPC and is calculated according to the simplified dosing regimen as shown in the table below:

Table 8: Simplified dosing regimen for intravenous iron derisomaltose

Hb (g/L)	Patients body weight <50 kg	Patients body weight 50 kg to<70 kg	Patients with body weight ≥70 kg
100 - 110	500 mg	1,000 mg	1,500 mg

<100	500 mg	1,500 mg	2,000 mg

Actual body weight will be used to calculate dose unless patients have a BMI greater than 30 when we will use an ideal body weight corresponding to a BMI of 25 (height in metres^2 x 25 = ideal body weight in kg). Maximum dose is 2,000mg as per dosing table above. Depending on the total amount of iron, the infusion will be administered in 250 mls 0.9% saline over either 15 minutes (iron dose ≤1,000 mg) or 30 minutes (iron dose >1,000 mg) and the participant will be monitored for hypersensitivity during and for at least 30 minutes following administration of the treatment. In addition, blood pressure and pulse will also be monitored before, during and after the infusion.

COMBINATION IRON AND ESA: Usual care plus a single dose of intravenous Ferric derisomaltose (approximately 20 mg/kg) plus a subcutaneous injection of darbepoetin (approximately 2 mcg/kg). Both IMPs will be administered before hospital discharge, as soon as possible after randomisation. Ferric derisomaltose will be administered first as described above. All patients will then immediately receive a standard darbepoetin dose of 150 mcg as a subcutaneous injection. This dose is pragmatic, represents a standard used in recent trials (Kong et al. 2022) and is the equivalent of approximately 40,000 IU of epoetin-alfa, the most common preparation used in previous perioperative trials (Spahn et al 2019 , Biboulet et al). This will ensure our results are comparable to the published literature, whilst also capitalising on the main advantage of darbepoetin (i.e. longer half-life) over other preparations.

Concomitant and Rescue Medications and Treatments

Throughout the trial, clinicians may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. All medications being continued by a patient on enrolment and all medications given in addition to the trial medication during the trial are regarded as concomitant medications and will be documented in the eCRFs.

Accepted concomitant treatments (not an exhaustive list):

- Antibiotics. Only allowed if prescribed for surgical postoperative prophylaxis.
- Blood transfusion (in accordance with local and national transfusion guidelines).

Prohibited concomitant treatments

- Oral iron is directly contraindicated in all patients post randomisation.
- Other preparations / doses of intravenous iron or ESA.

Compliance

Compliance with the interventions will be directly observed by the responsible healthcare professional administering the interventions. A record of administration will be made in the patient's medical notes and in the electronic Case Report Form (eCRF). Any reasons for non-compliance will be documented in the eCRF.

Accountability for drugs

The local pharmacy at each site will be accountable for the medications whilst in the department. These will be dispensed upon provision of a valid prescription form. Accountability will be monitored locally using routine drug accountability logs within the local pharmacy,.

Management of trial drug overdose

There are no specific antidotes or rescue medications. Adverse drug reactions will be treated in accordance with standard practice.

Urgent Safety Measures

Both trial IMPs have marketing authorisation and well characterised safety profiles thus urgent safety measures are not likely to be needed.

However, if an urgent safety measure is adopted, the MHRA will be notified in writing immediately and in any event no later than 3 days from the date the measures are taken. The sponsor and the relevant Research Ethics Committee (REC) will also be notified of the measures taken within the same time period. If needed, the sponsor will contact the MHRA Clinical Trials Unit and discuss the event with a safety scientist.

The DMC, in accordance with their charter, will be reviewing safety data at regular intervals throughout the trial and report any safety concerns as appropriate.

Protocol Deviations and Violations

Protocol non-compliance will be monitored via central monitoring of eCRF data. Where non compliances are detected, they will be reviewed by the TMG and recorded, and escalated to sponsor and other committees as required.

Where the outcome of the initial assessment is a serious breach or other serious protocol violation, it will be reported immediately to the CI and further investigated following the relevant NCTU SOPs.

The Chief Investigator will notify the Sponsor if a deviation or violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence, which may include reporting of a serious Good Clinical Practice (GCP) breach, internal audit of the trial and seeking counsel of the trial committees and the REC/MHRA.

Criteria for terminating trial

On the recommendation of the TSC, the sponsor (in collaboration with the TMG) may stop one or both of the trial comparisons if emerging evidence of efficacy or major safety concerns arise, or if there are significant concerns regarding trial conduct.

Stopping at one site will reflect unacceptable performance in recruitment or poor compliance with the protocol. In the case where a site closure has been decided due to inability to meet its recruitment target or due to poor compliance, the TMG may make this decision without consultation with the TSC.

LABORATORY ANALYSES

Blood tests will be carried out in the site NHS pathology departments. Data on, normal ranges etc. will be collected as part of site initiation and kept in the trial master file (TMF).

8. STATISTICS and DATA MANAGEMENT PLAN

DATA MANAGEMENT PLAN

The Data Management Plan (DMP) for this trial is a standalone document and is stored/maintained centrally within NCTU systems. . The DMP contains detailed information regarding data capture, queries, validation, cleaning and database lock and will be finalised prior to commencement of recruitment.

General

The DMP will include the agreed validation specification, roles and responsibilities for the trial data and user access, Additional manual and electronic reviews may also be conducted, and data queries / clarifications may arise from such reviews.

The trial database to be used is Research Electronic Data Capture (REDCap). It is a validated secure web-based platform which allows for data tracking via date stamped audit logs. POP-I participants will be identified on REDCap only by a unique participant identifier (their trial/participant ID) and initials to protect from bias and ensure confidentiality.

Data will be held on secure servers. These servers are located within The University of Nottingham data centres, which are managed and monitored regularly. Security is both physical (secure limited role-based access) and electronic (behind firewalls, access via user accounts (username and password) on encrypted connections, restricted access for some users (e.g. site staff) who only have access to their site patient data, and by user type/role). All access and data transactions will be logged in a full audit trail.

Data Capture and Data Queries

All trial data will be entered onto the trial specific database through the secure eCRF.
Data will be collected and entered by the research team and directly from participants who receive a secure link via a text message or email for online questionnaires. Participants who are unable or unwilling to complete online questionnaires will be offered alternatives to complete data (e.g. by post or telephone) and data will be entered into the database by either the NCTU trial team (i.e. data management team) or the local research team.

Only staff listed on the delegation log and training log will be given access to the relevant sections of the trial database e.g., site 1 staff will only have access to site 1 trial participants while the trial team including the research teams will have access to the wider database. Individual trial and research team member access will vary depending on role and associated blinding status.

Data reported on each eCRF will be checked for missing data or discrepancies and will be queried. Staff delegated to complete eCRFs will be trained to adhere to relevant aspects of GCP associated with data entry.

Data queries will not be raised on participant or parent/carer completed questionnaires.

Description of Data Entry Validation

Programmed validation and manual checks will be used to identify data anomalies. All programmed validation checks are documented in the data dictionary and data quality rules on the REDCap database.

Programmed validation checks will automatically flag discrepancies at the point of data entry or will be executed by data management at the point of data cleaning. Data identified as missing or having discrepancies, may require a manual data query to be raised within REDCap by the Data Management team at NCTU.

Data Cleaning and Database Lock

Once all data has been collected,is cleaned and signed off by the PI, the trial database will be locked. The database will be hard locked as per the relevant NCTU SOP using the associated checklist. All user rights will be removed, and it will be read only. Further details will be included in the trial DMP..

Monitoring

Monitoring activities for this trial are outlined in the trial Monitoring Plan.

STATISTICS

Methods

Analysis and reporting will be in accordance with the extension of the CONSORT 2010 Statement guidelines for the reporting of multi-arm parallel-group randomised trials. [70] The primary comparative analyses will be conducted according to randomised allocation, with due emphasis on confidence intervals for between-group comparisons. A detailed Statistical Analysis Plan (SAP) will be developed in accordance with guidelines prior to completion of data lock before data are unblinded and agreed with the TSC[74]. The primary approach to between-group comparative analyses will be by intention-to-treat, without imputation of missing outcome data. Descriptive statistics will be used to illustrate balance across the three groups at trial entry.

The primary comparative analysis will employ generalised linear mixed effects regression modelling to compare DAH30 between groups (each active treatment group versus usual care respectively) adjusting for minimisation factors and including random effects to adjust for clustering within surgery type and recruiting site, where technically possible. We will present the difference in means along with 95% confidence intervals for each primary comparison. If data for DAH30 show substantial departures from distributional assumptions, then alternative parametric distributions or non-parametric alternatives will be employed.

A secondary analysis for the primary outcome will employ zero-inflated beta-binomial regression (for each active treatment group versus usual care respectively), adjusting for minimisation factors. We will present an odds ratio and 95% confidence interval for each primary comparison in terms of the likelihood of:

a) returning home within 30 days
b) an additional day at home

Secondary outcomes will be analysed using mixed effects regression models dependent on data type (e.g., binary, continuous, time-to-event), adjusting for minimisation factors and

including random effects to adjust for clustering within surgery type and recruiting site, where technically possible.

Pre-specified subgroup analyses will be conducted for each primary comparison for the primary outcome to investigate whether the effect of each intervention is consistent across (i) types of surgery, (ii) postoperative baseline haemoglobin level, (iii) age groups, and (iv) sex, using the statistical test of interaction.

Statistical analyses will be carried out using Stata software version 17.0 (or later). All analyses involving disaggregate data will be conducted by an independent statistician, separate from the trial team.

No formal interim analyses are planned.

Sample size and justification

In order to detect a mean difference of 2 days in 'Days at Home at 30 Days' (DAH30) between an active treatment and the usual care control group, a total of 792 patients per group are required to achieve 90% statistical power. This is based on the following assumptions: a common standard deviation (SD) for DAH30 of 11, a two-sided 2.5% level of statistical significance (partitioned for two primary comparisons), and allowing for up to a conservative maximum of 5% non-collection of primary outcome data. The total sample size target (allocation ratio 1:1:1) is scaled up to 2,400 patients, 800 per group. Calculations were performed using PASS 2022 [75].

We acknowledge there is some uncertainty in the distribution of DAH30 in this patient population. For this reason, an SD of 11 was chosen as this is a conservative estimate based on the best available evidence, which suggests an SD of between 7.9 and 10 for similar patient populations. [58, 59]
While the sample size calculation assumes data are normally distributed, simulations for a broad range of scenarios including skewed log-normal data and zero-inflated distributions (allowing for up to 20% mortality before 30 days), indicate that for plausible departures from these assumptions, the planned sample size still provides adequate i.e., at least 80% statistical power. For further details please see Appendix I (*POP-I: Impact of departures from usual distributional assumptions on power*).

Because of the uncertainty surrounding these parameters, a review of the sample size calculation assumptions will be carried out during the internal pilot, and at the annual DMC meetings.

Assessment of efficacy

Table 9: Primary estimand

Estimand component	Definition
Population	Patients 60 years or older recovering from emergency laparotomy or hip fracture surgery
Endpoint	Days at Home at 30 days post-randomisation (DAH30)
Treatment conditions	1. Usual care 2. Usual care plus IV Iron

	3. Usual care plus IV Iron plus subcutaneous injection of ESA To assess the effect of: • Usual care plus IV Iron monotherapy (compared to usual care) • Usual care plus IV Iron plus subcutaneous injection of ESA combination therapy (compared to usual care)
Population level summary estimate	Difference in means
Intercurrent events	
Non-adherence to allocated treatment[1]	Treatment policy
Death	Composite strategy

[1]This includes any non-adherence to randomised allocation for any of the three groups (e.g., failure to initiate treatment or receipt of trial treatment inconsistent with randomised allocation).

For both active treatment comparisons with usual care control group respectively
The estimand for the primary outcome (DAH30) is the difference in means of the days alive and at home within 30 days of randomisation (with deaths scored as zero) between the intervention and usual care control group respectively, regardless of adherence to treatment, in participants 60 years or older recovering from major emergency surgery for whom we have follow-up data.

Assessment of safety

Safety data, including number of complications, treatment related Adverse events (AEs) and Serious Adverse Events (SAEs) will be summarised with descriptive statistics according to the treatment the participant received, irrespective of randomisation. Where a participant did not receive their allocated treatment but had a complication, treatment related AE or SAE this will be indicated.

The number of participants experiencing at least one complication, AE or SAE will be summarised using descriptive statistics. The total number and type of complications, AEs and SAEs will also be summarised, overall and by event.

Procedures for missing, unused and spurious data

The primary analysis for the primary and secondary outcomes will be based on participants with available data, without imputation of missing data. However, sensitivity analyses may be conducted which make different assumptions to investigate the potential impact of missing data. Full details will be specified in the statistical analysis plan.

Definition of populations analysed

The primary analysis population will be all randomised participants and will follow intention-to-treat principles (i.e., analysed as randomised regardless of adherence with allocation).

Adverse event data will be presented according to treatment received.

9. HEALTH ECONOMICS

Aim

An economic evaluation alongside the trial will be conducted to determine whether the treatment interventions within POP-I are cost effective compared to usual care alone at 120 days post-randomisation.

Methods

The health economic analysis will be conducted from a health and social care perspective. In addition, a broader perspective, to capture the effects on the individual and their families will be included. This will enable a broader societal perspective to be reported alongside a health service perspective in terms of the cost effectiveness of the interventions versus usual care.

Health care resource cost

Resources costs will be incurred within the hospital setting and once the patient is discharged from hospital. Cost collection will be from hospital records within hospital and rely on a purposely designed patient self-reported questionnaire post discharge to fully capture differential resource use post inpatient care.

Hospital treatment costs will be collected at each site for the treatment options of monotherapy (intravenous iron) and combined therapy (intravenous iron and ESA). Whilst the assumption is that these are incremental costs over and above usual care, to fully enable the analysis to incorporate all resources and outcomes across all the groups, it will be necessary to establish a hospital resource cost for the usual care group.

The hospital resource data collection would ask sites to indicate, for each treatment option, the grade of staff involved in the intervention, the time taken and which drugs were administered. This approach would give an estimate of direct treatment cost and range of possible costs. Where possible other direct hospital costs will be taken from hospital records as part of the trial recording.

A purposely designed patient health economic resource proforma (to be lodged In the UK health economists' DiRUM database) will enable the broad resource profile for the three treatment options to be recorded for the full follow-up profile for the patient group, particularly interventions and consequences of complications. This will include collection of secondary care, social care and primary care costs, alongside costs incurred by the patient and broader societal costs such as time lost from work. The proforma will be developed with Patient and Public Involvement (PPI) input and seek to minimise patient and family burden. Costs will be applied to resource use using data from sources such as NHS reference costs and the Unit Costs of Social Care (PSSRU Kent), alongside the detailed costing of interventions as outlined above. This enables the full economic consequences and costs of the treatment alternatives to be determined. Data will be collected at days 30 and 120.

Outcome Measures

Days at Home at 30-days (DAH30)

Days at Home at 30 days is an integer between 0 and 30 that represents the number of days the patient has spent at home since randomisation (day 0). DAH30 is the primary outcome measure for the trial.

Quality Adjusted Life Years (EQ-5D-5l)

The EQ-5D-5l enables a patient reported outcome to be used that will feed into the cost utility analysis. If necessary, the crosswalk index will be used to transform the 5L data to EQ-5D-3L data.

Analysis

The resource use data and subsequent calculation of health service and societal cost will be combined with the primary outcome (DAH30) and the EQ-5D-5L to provide a measure of the cost effectiveness and cost utility of the options against usual care. An incremental approach will be used and if appropriate the Incremental Cost Effectiveness Ratio (ICER) between the three groups plotted. In addition, an incremental net monetary benefit (iNMB) will be reported where a positive iNMB is deemed cost effective for a therapeutic option against the NICE £20–30k threshold. Cost Effectiveness Acceptability Curves (CEACs) showing the probability of effectiveness versus willingness to pay at the NICE threshold of £20–30k per QALY will be plotted.

10. ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE includes a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the trial.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure is an AE.
2. pre-existing disease or conditions present or detected at the start of the trial that did not worsen.
3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. disease or disorder being studied, or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. overdose of concurrent medication without any signs or symptoms.

Side Effects

Known side effects of the IMPs will be recorded directly within the eCRF. Adverse reactions will be reported from randomisation until discharge or 7 days post-randomisation, whichever is sooner.

All adverse events related to the hip fracture or emergency laparotomy and the underlying diagnosis, and standard surgical procedures will be recorded as complications on a 'complications case report form' within the eCRF and reported as secondary outcomes. Should any of these events meet the criteria for a SAE and fall within the SAE reporting period, they will also be reported as a SAE.

Serious adverse events (SAEs)

A Serious Adverse Event (SAE) is any adverse event occurring following trial mandated procedures, having received the IMP that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the trial IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment will be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

The below section does not pertain to expected AEs and SAEs reported as secondary endpoints (see section 6) which do not require expedited reporting with a trial SAE form. These events are secondary outcomes recorded in medical notes and collected as part of the eCRF, that will be routinely centrally monitored and reported.

All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the trial medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) will be informed immediately (within 24 hours) of any serious adverse events and will determine seriousness and causality in conjunction with any treating medical practitioners.

All serious adverse events will be reviewed throughout the trial by the TMG and the DMC and will be reported to the MHRA and REC as part of the annual Development Safety Update Reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Sponsor will ultimately be responsible for adverse event reporting.

SAE reporting procedure

On becoming aware that a participant has experienced an SAE, the PI (or delegate) must complete, date and sign an SAE Form. The form should arrive at the NCTU as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, the PI (or delegate) must email the SAE Form to:

nctu-sae@nottingham.ac.uk

On receipt, NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, the site will contact the NCTU. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the ISF.

For SAE forms completed by someone other than the local PI, the PI will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. A copy of the SAE form should be filed in the ISF.

PIs should also report SAEs to their own Trust in accordance with local practice.

Adverse event reporting period

Serious adverse events and treatment related adverse events will be reported from the point of randomisation until discharge from hospital or 7 days post-randomisation, whichever is sooner.

Urgent Safety Measures

Both trial IMPs have marketing authorisation and well characterised safety profiles thus urgent safety measures are not likely to be needed.

However, if an urgent safety measure is adopted, the MHRA will be notified in writing immediately and in any event no later than 3 days from the date the measures are taken. The sponsor and the relevant Research Ethics Committee (REC) will also be notified of the measures taken within the same time period. If needed, the sponsor will contact the MHRA Clinical Trials Unit and discuss the event with a safety scientist.

The DMC, in accordance with their charter, will be reviewing safety data at regular intervals throughout the trial and report any safety concerns as appropriate.

SUSARs

A serious adverse event that is either sudden in its onset (anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria must be treated as a SUSAR until deemed otherwise.

The event will be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial IMP.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed a SUSAR, will, within seven days, enter the required data on the MHRA's ICSR Submissions site.
- Will inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Will, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the trial protocol and inform the ethics and regulatory authorities as required.

Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP must be reported to the ethics committee that gave a favourable opinion as stated below.

The event must be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment will inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Will, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the trial protocol and inform the REC as required

Participant removal from the trial due to adverse events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the PI.

11. ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC/MHRA approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC/MHRA and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The PI or their nominee and the participant or other legally authorised representative will both sign and date the Consent Form before the person can participate in the trial.

The participant will receive a copy of the signed and dated forms and the original will be uploaded to REDCap. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the trial is entirely voluntary. The PI or their nominee will emphasize to the participant/legal representative that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The PI will inform the participant of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the ICFis amended during the trial, the PI will follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by Pharmacy. Accountability will be monitored locally using routine drug accountability logs within the local pharmacy, which will be subject to monitoring by the sponsor.

Standard hospital supplies will be used for IMP and sites will agree a dispensing flow appropriate to the local environment and working practices. PIs and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct trial medication. These records will be part of each patient's CRF

Case Report Forms

Each participant will be assigned a trial identity code number, allocated upon enrolment into the trial, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yy).

Participant contact details will be logged separately to the clinical eCRF data, to ensure participant identifiable data are separate to data used for analysis. The trial team may also use participant contact details to send out trial related questionnaires, correspondence and follow-ups, limited to the duration of the participant's participation in the trial. Participants may also consent to their contact details being retained beyond the duration of their participation in the trial, in order to be updated about the outcomes of the research or informed of future research.

The database will have in-built validation to ensure that the identifiers used all match with the allocated participant ID number. CRFs will be treated as confidential documents and held securely in accordance with regulations. The PI will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.
CRFs shall be restricted to those personnel approved by the Chief or local PI and recorded on the 'Trial Delegation Log.'

All paper forms will be filled in using black ballpoint pen. Errors will be struck through with a line, but not obliterated by using correction fluid. The correction should be inserted, initialled and dated as per GCP guidelines. The trial database has full automated auditing of all changes. The CI or local PI will sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents will be filed at the PI's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log will have access to trial documentation other than the regulatory requirements listed below. Where postal questionnaires are returned to NCTU they will be filed as source data as part of the TMF.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results will be made be available at all times for review by the Chief Investigator, Sponsor's designee and for inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and PIs will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and PIs and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

12. QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the TMF for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g., inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability and pharmacy records.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief Investigator or local PI will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The TMF and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor will take advice

from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the trial that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection, on request, by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

13. PUBLICATION AND DISSEMINATION POLICY

The research findings will be disseminated via a published HTA monograph in the NIHR Library, research papers published in high-impact, gold open-access, peer-review journals (trial protocol, primary clinical results and economic evaluation) and presentations at conferences, locally, nationally and internationally as detailed below. Results will be proactively communicated to groups involved in guideline development. They will also be made available via the specialist Colleges' and societies' websites, newsletters, a podcast and social media. Our two PPI representatives will lead on the dissemination of the trial results to patients and the wider public via a lay summary report, which will be made available in the trial sites and to trial participants and working with key charities such as Age UK and the Royal Osteoporosis Society.

We anticipate presentation of main clinical results at major international conferences such as Evidence Based Perioperative Medicine (EBPOM), the International Fragility Fracture Network and the Fragility Fracture Network UK. National presentations will be used to support dissemination and discussion (e.g. British Geriatric Society, Age Anaesthesia, Association of Surgeons of GB and Ireland, Emergency Laparotomy Collaborative, British Society of Haematology). Wherever possible, we will include our PPI partners in these presentations.

The results will be proactively and formally provided to:

- NICE for consideration of updates to the Hip Fracture Guidance (CG124, last formal update May 2017, minor update November 2019, update (types of surgery) 2022)
- British Society of Haematology, NHS Blood and Transplant
- National Emergency Laparotomy Audit (reviewed annually)
- National Hip Fracture Database
- British Orthopaedic Association Standards in Trauma (BOAST, last update 2019)
- Centre for Perioperative Care
- Drug licence holders with supporting data for amendment of indications for use of intravenous iron and / or erythropoietin in the perioperative period.

Website:

The project will have a dedicated website containing:

- Archives of trial documentation including trial protocol and statistical analysis plan
- Annual newsletters and trial progress reports
- Webinars, podcasts and recorded interviews with researchers and PPI
- Plain English and scientific summaries of results and their interpretation

Participants will not be identified in any publications.

We will co-develop our approach with PPI representatives from the UK Musculoskeletal Trauma PPI group and the NELA PPI group, which will continue their involvement throughout the trial. Depending on the results, we anticipate inclusion of the use of iron / ESA in patient-facing materials which are already in widespread use within hip fracture treatment and will work closely with the National Emergency Laparotomy Audit in the design of their patient-facing materials. We will also work with the Centre for Black and Minority Ethnic Health in Leicester to ensure development of inclusive public and patient-facing dissemination materials and strategies in multiple languages.

14. USER AND PUBLIC INVOLVEMENT

We have included two PPI co-applicants as full members of the project team and they have been involved in the development of the trial since inception. We have a formal system in place to support them in their roles and their time is fully costed to INVOLVE guidance.

Patient and Public advisory groups (PAG) have been consulted about preferred methodology and outcomes measurement in this trial. The PAG supported the use of DAH30 as the primary outcome measure and the methods of follow up.

We will continue to use the PAG representatives from the UK Musculoskeletal Trauma PPI group and the NELA PPI group when required to guide the trial.

Our PPI co-applicants have co-written and reviewed all patient facing documentation used in this trial, including Patient and Consultee Information Sheets, Consent forms, and letters. They will be assisting with trial dissemination and leading the dissemination of the trial findings to the public and media.

15. TRIAL FINANCES

Funding source

This trial is funded by NIHR (HTA Reference Number: NIHR133467)

Participant stipends and payments

Participants will receive a £15 shopping voucher at the time of issuing the 120-day questionnaire. Travel expenses will be offered for any hospital visits in excess of usual care.

16. SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) Iain M oppett

Signature: Iain Moppett (Oct 19 , 2023 17:46 GMT+1)

Date: Oct 19, 2023

Trial Statistician: (name) Mandy Jiang

Signature: Mandy Jiang (Oct 19, 2023 15:19 GMT+1)

Date: Oct 19, 2023

Trial Pharmacist: FILE NOTE: N/A NO TRIAL PHARMACIST ON TRIAL

Signature: N/A

Date: N/A

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Appendices

Appendix I: POP-I: Impact of departures from usual distributional assumptions on power

Appendix I:

POP-I: Impact of departures from usual distributional assumptions on power
27th January 2023

Introduction

The sample size calculation for POP-I assumes that the primary outcome – 'Days at Home at 30 Days' (DAH30) – is approximately normally distributed. A conservative estimate of the standard deviation (SD = 11) was employed in the calculation, partly to mitigate against misspecification of the sampling distribution[1]. In this document we present the findings of simulations to investigate the impact of departures from the distributional assumption on the power and type-I error of the trial.

Simulating DAH30 from a zero-inflated beta binomial distribution

A beta binomial model is used to simulate data for the usual care and an active intervention group (the equations and parameters are described at the end of the document). The variability is controlled by a dispersion parameter, σ. Other parameters were chosen to obtain a mean of approximately 20 in the control group (based on published data[1] for DAH30). A random sample (the proportion of which determined by the zero-inflation factor) is then set the zero.

Some examples of simulated DAH30 data are shown in Figure 1 and the impact of the dispersion parameter on the resulting standard deviation of the sample is described in Table 1. It is worthy of note that even for highly dispersed DAH30 data the sample SD is smaller than 11. Table 2 and Table 3 present the power and type-I error respectively for a range of distributional assumptions.

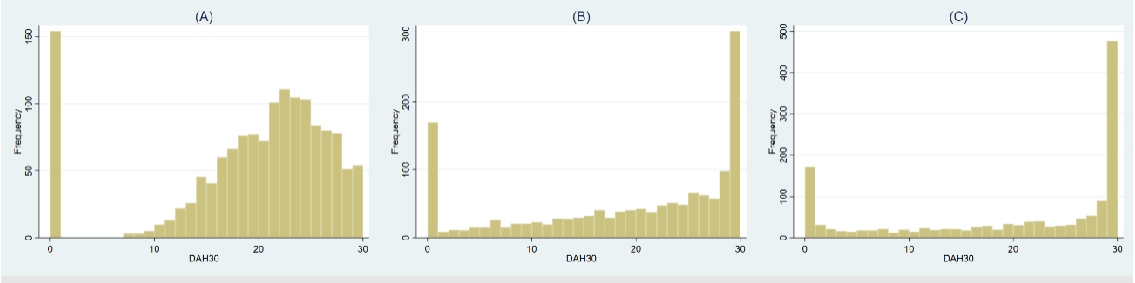

Figure 1: Example distributions for DAH30 with zero-inflation of 10% and varying the dispersion parameter: (A) σ =0.1, (B) σ =0.5, (C) σ =1.0. Approximate mean is 20 in the control group and 22 in the intervention group.

Table 1: Impact of chosen dispersion parameter on sample standard deviation

	(A)	**(B)**	**(C)**
Dispersion parameter	σ =0.1	σ =0.5	σ =1.0
Actual standard deviation	5.1	8.3	9.8

Table 2: Power to detect a difference in means of two days for data simulated from a zero-inflated beta binomial distribution using two analysis methods (i) linear model, (ii) zero-inflated beta binomial model.

		Power	
Zero-inflation	**Actual SD**	**Linear model**	**Zero-inflated beta binomial model**
σ = 0.1			
0%	5.1	100%	98%
10%	5.1	99%	99%
20%	5.1	85%	99%
30%	5.1	63%	99%
σ = 0.5			
0%	8.3	99%	85%
10%	8.3	90%	85%
20%	8.3	70%	86%
30%	8.3	55%	89%
σ = 1.0			
0%	9.8	95%	69%
10%	9.8	80%	70%
20%	9.8	62%	72%
30%	9.8	46%	70%

A beta binomial model is used to simulate data for the usual care and active intervention group. Variability is controlled by a dispersion parameter, σ. Other parameters were chosen such that the mean is approximately 20 in the control group and approximately 22 in the intervention group. A random sample (the proportion of which determined by the zero-inflation factor) is then set the zero.

(Continues next page)

Table 3: Type-I error for data simulated from a zero-inflated beta binomial distribution using two analysis methods with a specified type-I error of 2.5%, (i) linear model (ii) zero-inflated beta binomial model.

		Type-I error	
Zero-inflation	**Actual SD**	**Linear model**	**Zero-inflated beta binomial model**
σ = 0.1			
0%	5.0	2.7%	2.2%
10%	5.0	3.1%	2.7%
20%	5.0	2.8%	2.5%
30%	5.0	2.7%	2.3%
σ = 0.5			
0%	8.3	3.5%	2.6%
10%	8.3	3.1%	2.0%
20%	8.3	2.6%	2.9%
30%	8.3	2.7%	2.8%
σ = 1.0			
0%	9.8	2.1%	1.1%
10%	9.8	2.5%	1.1%
20%	9.8	2.6%	1.9%
30%	9.8	3.6%	1.6%

A beta binomial model is used to simulate data for the usual care and active intervention group. Variability is controlled by a dispersion parameter, σ. Other parameters were chosen such that the mean in both groups is approximately 20. A random sample (the proportion of which determined by the zero-inflation factor) is then set the zero.

Beta-binomial distribution

$$Y \sim \text{rbinomial}(30, Z)$$

$$Z \sim \text{beta}(\alpha, \beta)$$

$$\alpha = \frac{p}{\sigma}, \beta = \frac{1 -}{\sigma}$$

$$p = 0.4 + \frac{\exp(x)}{1 + \exp(x)}$$

$$x = -1 + \frac{1}{3} X_i$$

Where X_i is the group identifier (=0 for control group, =1 for the intervention group).

END