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Role of single-dose intravenous iron therapy for the treatment of anaemia after orthopaedic trauma: protocol for a pilot randomised controlled trial

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ABSTRACT

Introduction Orthopaedic trauma and fracture care commonly cause perioperative anaemia and associated functional iron deficiency due to a systemic inflammatory state. Modern, strict transfusion thresholds leave many patients anaemic; managing this perioperative anaemia is an opportunity to impact outcomes in orthopaedic trauma surgery. The primary outcome of this pilot study is feasibility for a large randomised controlled trial (RCT) to evaluate intravenous iron therapy (IVIT) to improve patient well-being following orthopaedic injury. Measurements will include rate of participant enrolment, screening failure, follow-up, missing data, adverse events and protocol deviation.

Methods and analysis This single-centre, pilot, double-blind RCT investigates the use of IVIT for acute blood loss anaemia in traumatically injured orthopaedic patients. Patients are randomised to receive either a single dose infusion of low-molecular weight iron dextran (1000 mg) or placebo (normal saline) postoperatively during their hospital stay for trauma management. Eligible subjects include adult patients admitted for lower extremity or pelvis operative fracture care with a haemoglobin of 7–11 g/dL within 7 days postoperatively during inpatient care. Exclusion criteria include history of intolerance to intravenous iron supplementation, active haemorrhage requiring ongoing blood product resuscitation, multiple planned procedures, pre-existing haematologic disorders or chronic inflammatory states, iron overload on screening or vulnerable populations. We follow patients for 3 months to measure the effect of iron supplementation on clinical outcomes (resolution of anaemia and functional iron deficiency), patient-reported outcomes (fatigue, physical function, depression and quality of life) and translational measures of immune cell function.

Ethics and dissemination This study has ethics approval (Oregon Health & Science University Institutional Review Board, STUDY00022441). We will disseminate the findings through peer-reviewed publications and conference presentations.

Trial registration number NCT05292001; ClinicalTrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our study is a single-centre, pilot, double-blind randomised controlled trial investigating the use of intravenous iron therapy (IVIT) for acute blood loss anaemia in injured orthopaedic patients.
⇒ Use of a single high-dose infusion of low-molecular weight iron dextran is a safe method of body iron store repletion that optimises study design logistics, patient capture, cost and efficacy of iron delivery.
⇒ We aim to assess the feasibility for a future large-scale randomised controlled trial evaluating IVIT as a means to improve time to anaemia and functional iron deficiency resolution as well as standardised patient-reported quality of life indices (Patient Reported Outcomes Measurement Information System, abbreviated PROMIS: fatigue, physical function, depression).

INTRODUCTION

Background and rationale: clinical

Acute blood loss in orthopaedic trauma and operative fracture care contributes substantially to perioperative anaemia and functional iron deficiency. The prevalence of preoperative anaemia has been observed as up to 50% in patients undergoing surgical stabilisation for hip fractures[1 2] and, unsurprisingly, up to 87% following hip fracture fixation.[2] Perioperative anaemia is associated with increased hospital length of stay (LOS), need for blood transfusion, risk of surgical site infection, genitourinary and cardiovascular complications and death.[1 2] Additionally, anaemia has clinical implications in quality of life (QOL) measures and is associated with fatigue, impaired physical performance, decreased exercise capacity and mood disturbances.[3–5] The broad impact of anaemia is often underestimated by clinicians; treatment may have profound benefits to patients' well-being.[4]

Therefore, evaluation and treatment of perioperative anaemia are critical to improving outcomes in orthopaedic surgery.

The standard of care for perioperative anaemia in orthopaedic trauma is packed red blood cell (pRBC) transfusion; however, this has been associated with increased mortality, nosocomial infection, postoperative venous thromboembolism, multisystem organ dysfunction and acute respiratory distress syndrome.[1 6 7] Current recommendations for the treatment of anaemia in orthopaedic trauma centre on a restrictive strategy for management (ie, haemoglobin <7 g/dL for pRBC transfusion initiation) to minimise transfusion reactions while ignoring the long-term recovery effects of anaemia. A safer alternative to pRBCs is desirable because a critical number of patients do not meet this restrictive transfusion threshold and may be negatively impacted by anaemia during recovery.

Currently, there is no standard practice of iron supplementation for treatment of anaemia in the acute trauma setting. Previous studies have shown promising results for the use of intravenous iron therapy (IVIT) in orthopaedic patients. A recent meta-analysis by Shin *et al* concluded that use of IVIT perioperatively in orthopaedic surgery significantly decreased the proportion of patients receiving pRBC transfusions by 31%, shortened hospital stay by 1.6 days and reduced postoperative infection rate by 33%.[6] Serrano-Trenas *et al* demonstrated that intravenous iron sucrose therapy reduced transfusion requirements in a subset of geriatric hip fracture patients without differences between groups for morbidity, mortality or LOS.[8] Ten per cent of the patients enrolled in the studied died prior to their posthospitalisation check-up. Additionally, only 16% of patients in the investigational arm received the three full doses of IVIT sufficient to replete body iron stores. Shortcomings in study design and restrictive study population limit the utility of the findings in this study. Non-orthopaedic studies suggest improved patient-reported outcomes with IVIT after haemorrhagic events.[3 9] Unfortunately, there are a lack of high-quality randomised controlled trials (RCT) in the orthopaedic literature investigating the routine use of IVIT. Furthermore, no studies within orthopaedics have looked at the effect of IVIT on patient-reported QOL outcomes.

Background and rationale: translational

Our preliminary analysis of iron store derangements following a traumatic event has prompted us to simultaneously investigate the underlying pathophysiology of anaemia during the inflammatory conditions of trauma and surgery. We have found that less than 5% of patients demonstrated normal serum iron, total iron binding capacity, transferrin saturation and transferrin values following orthopaedic fracture care, with abnormally low values in some or all of these assessments being seen in the vast majority of patients. Despite this, ferritin level is normal in approximately two-thirds of patients overall and normal or high in nearly all patients with all other iron studies low.[10] This phenomenon may indicate that iron becomes sequestered and unavailable for use in replenishing blood cell volume in the setting of orthopaedic trauma, leading to a state of functional iron deficiency.

The consequence of functional iron deficiency, in which insufficient iron is available for erythropoiesis despite normal iron stores in bone marrow macrophages[11 12] has not been fully investigated in the trauma and orthopaedic settings. Functional iron deficiency results from two main pathways—conditions that incite a systemic inflammatory response (ie, surgery, trauma)[6 13] and situations of increased erythropoiesis mediated by endogenous or exogenous erythropoietin stimulation.[13] In the former, there is a hepcidin-mediated down regulation of intestinal iron absorption and impaired mobilisation of body iron stores.[14] In the latter, there is a mismatch between iron demand and supply as in the setting of acute blood loss.[13] Both of these clinical scenarios play a role in the setting of orthopaedic trauma requiring operative surgical stabilisation.

We aim to evaluate the consequence of IVIT on immune cell physiology given the connection of functional iron deficiency to proinflammatory states. The general effect of these cells on bone regeneration in the setting of fracture is three-fold; they promote migration and proliferation of osteogenic cells, increase blood vessel formation and induce inflammatory reactions.[15 16] During fracture repair, multiple immune cell types work in harmony to modulate healing, including those of myeloid origin (neutrophils, macrophages, osteoclasts) and lymphoid origin (T-lymphocytes and B-lymphocytes, natural killer cells).[16] Further work must be done to understand the biological significance of immune cells and their regulatory factors in bone regeneration as well as potential areas for modulation.

Platelets are of particular interest to investigate as they not only affect wound healing but also play a critical role in surgical haemostasis. Platelet production is known to be intimately linked with iron stores, as iron deficiency often causes increased platelet counts, however the role of iron in platelet function remains unclear. While platelet numbers increase in anaemia, platelet response to inflammation, trauma and conditions with excessive bleeding are more complex—where platelet activities cause increased clotting as well as exacerbate bleeding.[17] Low but persistent levels of platelet stimulation in inflammation and trauma can cause a dulling of platelet activity (ie, platelet exhaustion).[17 18] Specific mechanisms of platelet dysfunction under these conditions remain largely unspecified.[19–21]

Recent work by our multidisciplinary team has identified several clinically relevant physiologic changes of platelets in iron-deficient premenopausal women which are reversed with IVIT. Preliminary findings demonstrated (1) intravenous iron repletion decreases platelet count in iron deficiency, (2) iron repletion significantly increases platelet integrin activation and alpha-granule secretion in response to adenosine di-phosphate (ADP)

and collagen-related peptide and (3) platelet adhesion to type-1 collagen is enhanced after IVIT.[22] This suggests that iron is vital for optimal platelet function and haemostasis. We seek to understand that the alterations IVIT has on similar platelet profiles in injured patients, which has not previously been studied.

Objectives and study hypothesis

The primary objective of this study is to determine feasibility of study design, recruitment, randomisation, intervention implementation, blinded procedures and follow-up. Feasibility outcomes will be quantified as rate of participant enrolment (60 patients randomised in 2 years), proportion of participants completing each follow-up visit, proportion of missing data, rate of transfusion reactions and rate of protocol adherence. The primary clinical outcome is patient-reported QOL measures of fatigue on PROMIS questionnaire. The central hypothesis motivating the research is that acute blood loss anaemia may be one modifiable risk factor which can be addressed with IVIT to improve patient well-being following traumatic orthopaedic injury. The secondary objectives of the study include:

(1) Measure the time to return to normal haemoglobin as a marker for resolution of anaemia and normalisation of body iron stores as a marker for resolution of functional iron deficiency following orthopaedic fracture care.

(2) Evaluate the effect of IVIT on patient-reported QOL measures of physical function and depression following traumatic orthopaedic injury through standardised PROMIS questionnaires.

(3) Appraise cost-effectiveness of IVIT with a cost-utility analysis using quality-adjusted life years (QALYs).

(4) Determine the role of IVIT on immune cell physiology in the setting of acute blood loss anaemia and inflammation from orthopaedic trauma.

METHODS AND ANALYSIS

Overview of study design

This is a single-centre, double-blind parallel design RCT investigating the use of IVIT (N=30) compared with placebo (N=30) for acute blood loss anaemia in traumatically injured orthopaedic patients. The intervention consists of a single dose infusion of low-molecular weight iron dextran (1000 mg LMW ID) postoperatively during the patient's hospital stay for initial trauma management. Patients in the placebo arm are given an equal volume normal saline infusion (figure 1). Both the investigator and participants are blinded to the study treatment administered.

Eligibility criteria

Inclusion criteria

1. Patients age 18–89 admitted with a lower extremity or pelvis fracture requiring surgical stabilisation.
2. Acute blood loss anaemia as defined by haemoglobin concentration between 7.0 and 11.0 g/dL within 7 days postoperatively from definitive fracture stabilisation during the hospital admission.

Exclusion criteria

Patients who meet any one or more of the following will be excluded from the study:

1. History of intolerance or hypersensitivity to intravenous iron supplementation.
2. Active haemorrhage requiring greater than two units (whole blood or pRBCs) transfused perioperatively.
3. Multiple planned operative procedures during the trauma admission, excluding orthopaedic staged procedures for the fracture meeting inclusion criterion one (such as temporising external fixator application and washout for open fracture) in which subjects otherwise meet qualifications for enrolment after definitive stabilisation.

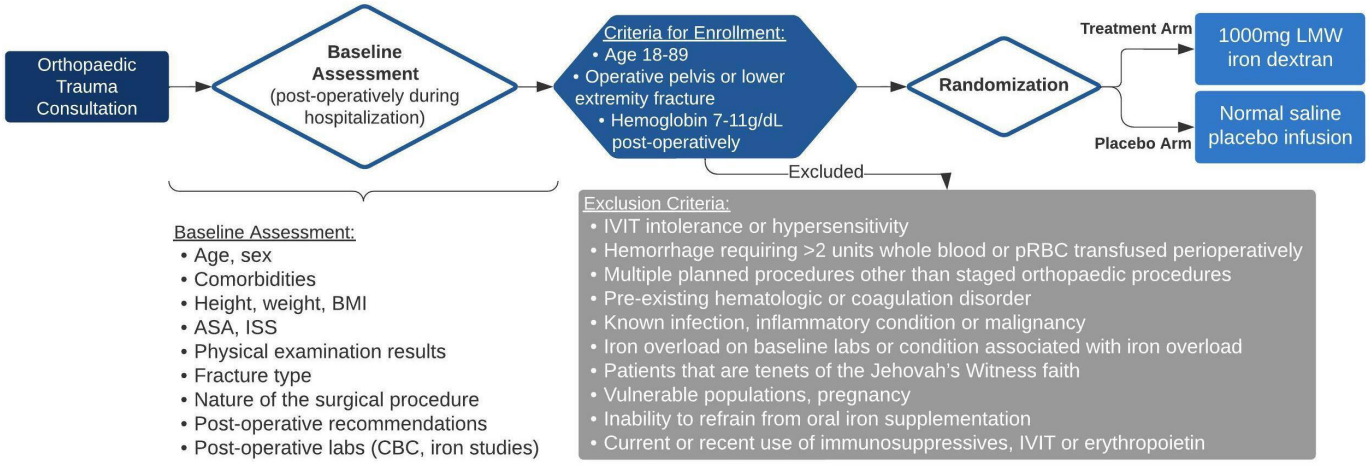

Figure 1 Study design flowchart. ASA, American Society of Anesthesiologists Score; BMI, body mass index; CBC, complete blood count; ISS, injury severity score; IVIT, intravenous iron therapy; LMW, low-molecular weight.

4. Pre-existing haematologic or coagulation disorder (eg, thalassemia, sickle cell disease, haemophilia, von Willibrand's disease or myeloproliferative disease).
5. Diagnosis of chronic kidney disease and/or chronic liver disease.
6. Known infection, inflammatory condition (eg, systemic lupus erythematosus, rheumatoid arthritis and ankylosing spondylitis) or malignancy.
7. Pregnancy.
8. Iron overload (defined as serum ferritin concentration ≥1000 ng/mL, serum iron concentration >160 µg/dL or serum transferrin saturation ≥50%) or any condition associated with iron overload (eg, hemochromatosis and aceruloplasminemia).
9. Patients who are tenets of the Jehovah's Witness faith.
10. Vulnerable populations including paediatric patients, geriatric populations 90 or older, incarcerated individuals, those unable to provide informed consent.
11. Inability to refrain from oral iron supplementation during study period.
12. Current or recent (within 30 days) use of immunosuppressive agents.
13. Use of any IVIT or recombinant human erythropoietin formulation within the previous 30 days.

Study intervention and blinding

The study intervention consists of a single-dose infusion of LMW ID (1000 mg LMW ID). Patients in the placebo arm are given an equal volume normal saline infusion (250 mL NS). Given the dark colour of the LMW ID compared with the clear, translucent normal saline, opaque bags and tube covers will be used in order to blind all study staff and patients to the allocated treatment group. The blinding covers will be applied by an unblinded pharmacist who prepares the infusion and remain in place during transport, infusion and disposal of the infusion packaging.

LMW ID was chosen over intravenous iron alternatives to optimise logistics, patient capture, cost and efficacy of iron delivery. LMW ID has a stable formulation for safe administration of sufficient iron for repletion of body iron stores in a single high-dose infusion over 1 hour, as compared with alternative regimens that require several small-dose administrations over the course of days to weeks.[23 24] Use of this iron formulation improves on prior RCTs with incomplete adherence when using multiple infusions of alternative low-dose regimens. Importantly, the Food and Drug Administration has recognised the incidence of life-threatening adverse effects and deaths associated with IVIT (2.2 per million doses and 0.4 per million doses, respectively) is significantly lower than that associated with blood transfusion (10 per million units and 4 per million units, respectively).[14] Oral iron supplementation is an alternative to IVIT but is associated with increased risk of adverse reactions,[23] poor medication adherence,[13 23] lower efficacy[13] and limited use in settings where rapid iron repletion is required.[13 14] IVIT is preferred when rapid, significant correction is necessary as it has higher efficiency and shorter time to improvement.[14 25 26]

Research Pharmacy Services (RPS) at our institution is responsible for all study drug-related tasks including randomisation and blinding of the study drug and placebo. RPS follows a published protocol for drug shipment/receipt, packaging, storage, preparation, dispensing and accountability and administration. Consent will be required from the patient or a legally authorised representative. Unblinding will be considered in emergency situations (ie, severe infusion reaction). Verbal permission from the principle investigator or coinvestigator will suffice in order to unblind, followed by subsequent written documentation after the unblinding has occurred. Drug destruction will be performed by RPS at the study drug expiration date or the completion of the study. Given the single-dose design of the study drug, medication compliance assessment will not be required; however, it will be documented if the treatment had to be discontinued prior to completion of infusion due to adverse reaction.

Recruitment

Our institution is a level 1, tertiary care centre with high volume fracture care and over 4000 trauma activations yearly. Our recruitment pool consists of all patients admitted with orthopaedic trauma during the enrolment period, planned June 2022 through May 2024. Patients are eligible for enrolment if they meet the aforementioned criteria within 7 days postoperatively from definitive surgical stabilisation of their fracture. Screening includes review of laboratory studies, injuries and comorbidities to assess for inclusion.

Allocation of patients to study groups

Following informed consent, patients are randomised one-to-one into a treatment arm by RPS and receive the allocated therapy via a computer-generated random number schema from randomisation.com. RPS is responsible for all blinding procedures. Medication-related study documents are stored in an electronic pharmacy binder on Vestigo only accessible by unblinded personnel. The study medication is stored with restricted access in the hospital inpatient pharmacy and prepared, delivered, labelled and covered with blinding bags and tubing covers by the unblinded pharmacy personnel on subject enrolment to ensure that both the investigators and subjects are blinded to the treatment received.

Outcome measures

Feasibility outcome measures

Appraisal of feasibility will be based on rate of participant enrolment per year, rate of screening failures, proportion of participants completing each follow-up visit, proportion of missing data, rate of transfusion reactions and rate of protocol adherence. Other feasibility concerns will be qualitative in nature, including documentation of blinding failures, review of challenges in recruitment and

Table 1 Schedule of enrolment, study drug allocation, quality of life and laboratory assessments

Time point	Enrolment	Allocation	Follow-up			
	POD1 through POD7 during hospitalisation		2 weeks	4 weeks	6 weeks	3 months
Screening/enrolment						
Eligibility screen	x					
Informed consent	x					
Randomisation		x				
Allocation of study drug vs placebo		x				
Assessments						
PROMIS Fatigue	x		x	x	x	x
PROMIS Physical Function	x		x	x	x	x
PROMIS Depression	x		x	x	x	x
EQ-5D-5L	x		x	x	x	x
Laboratory studies						
CBC	x		x	x	x	x
Ferritin	x		x	x	x	x
Iron, TIBC, transferrin, %sat	x					x
Immune cell studies	x		x	x	x	x

CBC, complete blood count; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; POD1, postoperative day 1; PROMIS, Patient-Reported Outcomes Measurement Information System; %Sat, transferrin saturation; TIBC, total iron binding capacity.

retention and assessment of data management and survey administration.

Primary clinical outcome

The primary clinical outcome of this pilot study will be Health-Related Quality of Life (HRQoL) over the 3 months postoperatively. HRQoL will be assessed using the PROMIS Fatigue Questionnaire, a computer adaptive survey (table 1). This will measure feelings of tiredness likely to decrease one's ability to execute daily activities and function normally in family or social roles.

Secondary clinical outcomes

Outcome measures to fulfil the secondary objectives will be collected to assess the feasibility of their collection and relevance of timing in anticipation of a future large-scale RCT.

Laboratory data

- *Complete blood count*: concentration of haemoglobin (oxygen carrying protein) in whole blood and percentage of blood volume (haematocrit) occupied by RBCs are of primary interest. These are markers of anaemia (defined as haemoglobin <12 g/dL in women and <13.5 g/dL in men) measured for inclusion assessment and to monitor for resolution of anaemia at all study follow-up visits.
- *Ferritin:* evaluated at enrolment to assess for iron overload (patients with a ferritin level ≥1000 ng/mL will be excluded) and tracked throughout the study to measure participants' body stores of iron. Importantly, patients will not be required to have a ferritin level consistent with iron deficiency (≤50 ng/mL) as we have observed that the majority of patients have normal (51–200 ng/mL) to high (>200 ng/mL) post-traumatic ferritin levels.
- *Additional iron studies (serum iron, transferrin, total iron binding capacity*). Additional indicators of body iron stores and iron-carrying capacity within blood. Utilised to further define patients' anaemia and iron available for functional use. Similar to ferritin level, only patients with iron values consistent with overload on postoperative laboratory work will be excluded (as defined by exclusion criterion 8).

QOL measures

- *PROMIS Fatigue Questionnaire:* computer adaptive survey administered via REDCap to evaluate feelings of tiredness likely to decrease one's ability to execute daily activities and function normally in family or social roles.
- *PROMIS Physical Function Questionnaire:* computer adaptive survey administered via REDCap to measure self-reported capability to perform physical activities including activities of daily living.
- *PROMIS Depression Questionnaire*. Computer adaptive survey administered via REDCap to assess negative mood, views of self, social cognition and decreased social engagement.
- *EQ-5D-5L Quality of Life Questionnaire:* instrument assesses HRQoL with five dimensions of health, each with five levels ranging from no problem (level 1) to extreme problem (level 5). Answers correspond

to 3125 possible health states that can be converted into a single 'utility' score. This will be used for the assessment of QALYs and cost-effectiveness of IVIT for the treatment of acute blood loss anaemia following surgical fracture stabilisation.

Immune cell functional testing will be performed through a variety of novel laboratory techniques, including but not limited to the following

- Flow cytometry and fluorescence-activated cell sorting to quantify and evaluate platelets, cytokines and other immune cells.[27]
- Assessment of platelet aggregation under venous shear in chambers coated with type I collagen.
- Use of proteomics tools to systematically measure the molecular composition of immune cells as well as the activation of signalling systems in response to relevant agonists.[28]
- Analysis of immune cells, biomarkers and relevant circulating factors using Luminex technology and ELISA.

Participant timeline

Table 1 delineates the schedule for enrolment, interventions, laboratory studies and patient-reported outcome surveys.

Safety considerations

Adverse events are documented in a secure REDCap database, including description of the symptoms, management provided and outcome. Adverse events are categorised as mild, moderate and severe in relation to the infusion itself as described hereafter. Patients are additionally monitored at all follow-up visits for other complications in their care (not necessarily related to study drug administration) including fracture-related infection (FRI), nonunion and need for postinfusion pRBC transfusion per clinical threshold criteria. Infections will be determined using the criteria for FRI as validated by Metsemakers *et al*[29]

Serious adverse events including severe infusion reactions (eg, cardiac arrest, cyanosis, loss of consciousness, periorbital oedema, wheezing, stridor) will be reported as required by the IRB. Management of such events will include stopping the infusion, activating the rapid response team, oxygen supplementation, epinephrine, intrvenous steroids, and initiating advanced cardiac life support (ACLS) (if necessary).

Other infusion-related reactions are documented and managed as described by DeLoughery and Rampton *et al* (figure 2).[23 30] Hypersensitivity medications are ordered with the study medication per our standard institution order set, including diphenhydramine, famotidine, hydrocortisone sodium succinate injection, epinephrine IM and normal saline bolus.

Procedures for completion

Completion occurs at the last follow-up visit when all patient-reported outcome measures and laboratory data have been collected. In an effort to optimise retention, PROMIS surveys will be emailed to study participants via REDCap (which has prebuilt computer adaptive testing for the chosen instruments) at the appropriate follow-up timepoints. These may be completed on email receipt or during scheduled study visits. Therefore, patient report outcomes may still be completed virtually in the event patients are otherwise unable to complete in person follow-up visits. Patients may freely withdraw their informed consent at any time during the clinical trial. Furthermore, the investigator may terminate a subject's participation in the research study if they are found to have any of the exclusion criteria during the study period (including use of oral iron supplements, new malignancy or newly diagnosed inflammatory disease) with the exception of postoperative infection. Subjects are considered lost to follow-up if they do not attend scheduled study visits or complete study surveys.

Sample size consideration

The primary objective of this study is to pilot for feasibility; therefore, traditional quantitative sample size calculations are not well suited for this study. Given the exploratory nature of pilot studies, we plan to enrol a sample of 60 patients to assess the feasibility of a definitive large RCT.

Based on prior studies, a significant increase from baseline haemoglobin of 1.2 g/dL±1.4 was observed within a median follow-up time of 3 weeks after administration of LMW ID.[31 32] The minimum number of subjects required to detect a clinically meaningful change in PROMIS instrument score defined as five points with a SD of 10 (minimally important change has been defined for several PROMIS measures as 3–6 points[33]). However, the results of this pilot study will ultimately inform sample size requirements in a larger scale RCT.

Data analysis plan

Analysis of feasibility outcomes

Rate of participant enrolment per year, percentages of screening failures and proportions of completed follow-up visits and missing data will be summarised as counts with percentages or means with SD.

Analysis of clinical outcomes

The intervention arm (IVIT) will be compared with the placebo for all prespecified analyses. We will use haemoglobin as a marker for resolution of anaemia, as defined as >12 g/dL in women and >13.5 g/dL in men. Based on previous studies, administration of IVIT improves haemoglobin levels within the first week, and normalisation is typically achieved within 3–4 weeks.[1] We anticipate that this will hold true in our IVIT cohort, with resolution of anaemia occurring around 3 months for the placebo cohort. We will evaluate for statistical difference of change in haemoglobin at all study visit timepoints with t tests.

We will use PROMIS fatigue, physical function and depression scores as indicators of important QOL metrics

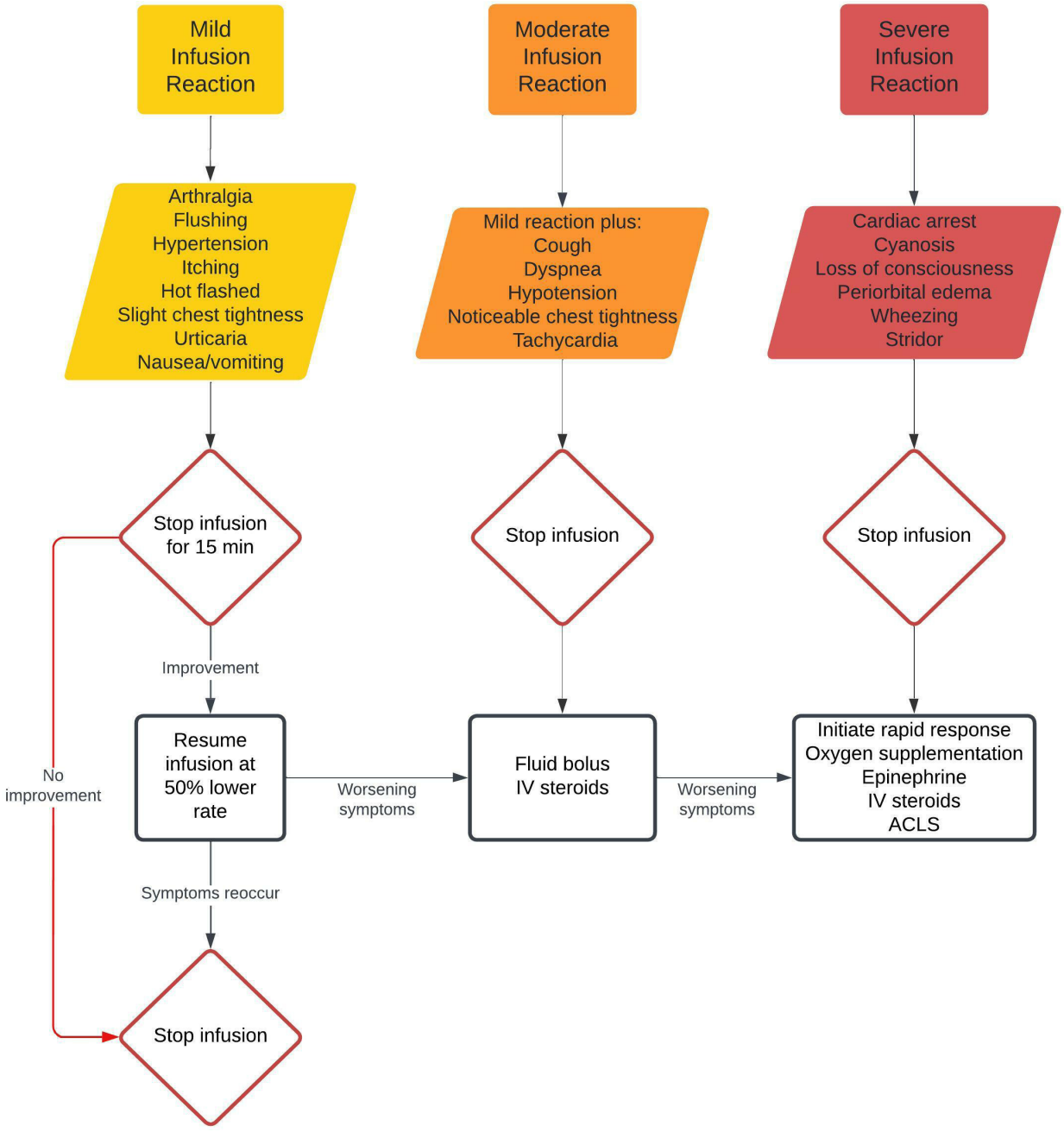

Figure 2 Infusion reaction treatment algorithm. ACLS, advanced cardiac life support.

that relate to recovery from traumatic injury and fracture healing. The aggregated change in PROMIS score will be calculated as a per cent change from baseline at all time points for both measures. An analysis of covariance model will be used to access for clinical significance, with treatment (IVIT vs placebo) as factors and baseline score as covariate.

We will perform a multivariate analysis adjusting for the potential confounders of age, sex, Body Mass Index (BMI) and transfusion status (transfusion vs no transfusion) known to contribute to anaemia, fatigue and depression. Both unadjusted and adjusted results will be reported. Analysis will be performed according to a modified intention-to-treat paradigm in which all patients, except those who are deemed ineligible after randomisation, will be analysed according to the treatment group to which they are randomly assigned.

Given the investigative nature of pilot studies, we plan to additionally conduct several exploratory analyses to inform the definitive trial analysis. Participants will be placed in subgroups based on transfusion requirements. We will compare patients who received perioperative blood transfusions (whole blood or pRBCs), not exceeding two units, to those who do not. These subgroups will be assessed for change in haemoglobin with t tests and analysis of variance. Bivariate linear regression analyses will assess the relationship between patient factors, injury characteristics as well as recovery parameters (age, sex,

postoperative weightbearing status, fracture type, fixation type, length of hospital stay, degree of iron panel derangements, degree of postoperative anaemia and transfusion requirements) and fatigue, physical function and depression questionnaires PROMIS scores.

We will use multiple imputation to handle missing data. Pilot studies are exploratory in nature and will be underpowered for clinical outcomes due to sample size, and multiple testing will not be adjusted for. Therefore, all clinical pilot study data should be interpreted as exploratory. Significance level set to 95% for all statistical measures. Statisticians blinded to treatment arms will conduct all analyses in the most updated version of R (R Core Team).

Potential impact of study

Successful completion of this project has the potential to provide relevant clinical information for the development of a large-scale, multicenter randomised trial. Ultimately, a better understanding of the effects of IVIT both clinically and at a biological level may alter our treatment approach of anaemia in patients who sustain orthopaedic injuries, thereby leading to decreased risks and improved recovery. If IVIT is proven to be effective in improving QOL after traumatic lower extremity fracture, clinical relevance to other fracture types and more broadly in orthopaedic surgery will follow. We plan to further evaluate the efficacy of IVIT for reduction of blood transfusion and as an adjunct therapy to blood transfusion in the future.

Patient and public involvement

Patients and the public will not be involved in the design, conduct, reporting or dissemination plans of this pilot research protocol. Patient feedback from participation in this study will be considered on finalising a definitive large-scale study.

Ethics and dissemination

Research ethics approval: this study has ethics approval from the Oregon Health & Science University Institutional Review Board (STUDY00022441). Protocol modifications and annual continuing review will be submitted as necessary for IRB approval prior to implementation and continuation of the study, respectively.

Consent: informed consent is performed using IRB approved forms with a trained study provider. Patients may freely withdraw their informed consent at any time during the clinical trial.

Confidentiality: all data from this work are maintained in security and confidentiality at our institution. A secure REDCap database (encrypted and password protected) is used for data collection, administration of PROMIS surveys, organisation of data reports for statistical analysis and documentation of adverse events. Research medication management, randomisation, blinding and related record keeping is performed by RPS per their published protocol.

Dissemination policy: the findings of this study will be disseminated through peer-reviewed publications and conference presentations. This protocol has been reported following the Standard Protocol Items: Recommendations for Interventional Trials statement.[34] Results will be published following the Consolidated Standards of Reporting Trials guidelines for pilot and feasibility trials.[35 36] In addition, appropriate publication requirements will be upheld for the use of PROMIS instruments.

Contributors DFP and ZMW are co-principle investigators responsible for conceptualisation and funding of the study. DFP further designed and drafted the protocol for the study. DMF, GJD, NJW, JJS and JEA contributed to study design as pertinent to their respective specialties, providing specific content and edits to the manuscript. MAS acted as an advisor to the project and edited the manuscript. NSM, CEH and KL oversee the clinical aspects of the study and CJY oversees the translational laboratory component. NSM additionally provided guidance for planned statistical analysis. All authors have reviewed and approved the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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