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Clinical Trial Protocol

CLINICAL TRIAL PROTOCOL

Postoperative intravenous iron to treat iron-deficiency anaemia in patients undergoing cardiac surgery: a protocol for a pilot, multicentre, placebo-controlled randomized trial (the POAM trial)

Justyna Bartoszko[1,2,3,4,5,*,†], Sarah Miles[2,†], Saba Ansari[2,3], Deep Grewal[2,3], Michelle Li[1,2], Jeannie Callum[5,6], Stuart A. McCluskey[2,3,4], Yulia Lin[5,7,8] and Keyvan Karkouti[1,2,3,4,5,9,10]

[1]Institute of Medical Science, University of Toronto, Toronto, ON, Canada, [2]Department of Anesthesia and Pain Management, Sinai Health System, Women's College Hospital, University Health Network, Toronto, ON, Canada, [3]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada, [4]Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada, [5]University of Toronto Quality in Utilization, Education and Safety in Transfusion Research Program, Toronto, ON, Canada, [6]Department of Pathology and Molecular Medicine, Kingston Health Sciences Centre and Queen's University, Kingston, ON, Canada, [7]Precision Diagnostics and Therapeutics Program, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [8]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada, [9]Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada and [10]Interdepartmental Division of Critical Care, Department of Medicine, University of Toronto, Toronto, ON, Canada

*Corresponding author. Institute of Medical Science, University of Toronto, Toronto, ON, Canada. E-mail: Justyna.Bartoszko@uhn.ca
†Co-first author.

Abstract

Background: Iron-deficiency anaemia, occurring in 30–40% of patients undergoing cardiac surgery, is an independent risk factor for adverse outcomes. Our long-term goal is to assess if postoperative i.v. iron therapy improves clinical outcomes in patients with preoperative iron-deficiency anaemia undergoing cardiac surgery. Before conducting a definitive RCT, we first propose a multicentre pilot trial to establish the feasibility of the definitive trial.
Methods: This internal pilot, double-blinded, RCT will include three centres. Sixty adults with preoperative iron-deficiency anaemia undergoing non-emergency cardiac surgery will be randomised on postoperative day 2 or 3 to receive either blinded i.v. iron (1000 mg ferric derisomaltose) or placebo. Six weeks after surgery, patients who remain iron deficient will receive a second blinded dose of i.v. iron according to their assigned treatment arm. Patients will be followed for 12 months. Clinical practice will not be otherwise modified. For the pilot study, feasibility will be assessed through rates of enrolment, protocol deviations, and loss to follow up. For the definitive study, the primary outcome will be the number of days alive and out of hospital at 90 days after surgery.
Ethics and dissemination: The trial has been approved by the University Health Network Research Ethics Board (REB # 22-5685; approved by Clinical Trials Ontario funding on 22 December 2023) and will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practices guidelines, and regulatory requirements.
Clinical trial registration: NCT06287619.

Keywords: anaemia; infusions; intravenous; iron deficiency; iron compounds; perioperative care

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Strengths and limitations of this study

- This is the first proposed RCT assessing postoperative i.v. iron therapy to treat iron-deficiency anaemia in patients undergoing cardiac surgery.
- This internal pilot trial will ensure that a large, definitive RCT is feasible and will offer preliminary data allowing for refinement of trial procedures, including the definitive trial's sample size, if required.
- The primary outcome for the definitive study will be the number of days alive and out of hospital at 90 days after surgery, which is an objective, patient-centred measure of overall recovery, health, and quality of life after surgery that is highly sensitive to changes in surgical risk and complications.
- If postoperative i.v. iron is shown to be efficacious and safe in the definitive study, this will greatly expand treatment for postoperative anaemia after cardiac surgery and likely improve patient-important outcomes.
- As this is a pilot study, it is not powered to measure the effectiveness of i.v. iron therapy after cardiac surgery and is limited in terms of estimation of product safety in this context.

Chronic anaemia, defined as a haemoglobin concentration below 120–130 g L^{-1} for >3 months,[1–4] is present in 30–40% of patients undergoing cardiac surgery.[2,5,6] The presence of anaemia is a strong, independent risk factor for adverse outcomes; the *risk-adjusted* odds of death, major organ dysfunction, infection, prolonged hospitalisation, and readmission after cardiac surgery are up to four-fold higher in anaemic than in non-anaemic patients.[6–15] The primary cause of chronic anaemia in cardiac surgical patients is iron-deficiency anaemia, which occurs when the supply of iron to the bone marrow is impaired.[2,5,16,17] Because of the significant blood loss involved in most cardiac surgical procedures, iron-deficiency anaemia is further exacerbated for several weeks to months after surgery, with a profound systemic inflammatory response that worsens iron sequestration and a state of acute-on-chronic anaemia that increases erythropoiesis demand to a degree that can outstrip the available iron supply.[18–22]

Oral iron supplements are often not effective in surgical patients as they are poorly tolerated because of side-effects,[23] and have low bioavailability (10–20% absorption rate),[24,25] which means that weeks to months of therapy are required to replenish iron stores. Often, the luxury of significant lead time before cardiac surgery is not available. I.V. iron formulations, however, have superior side-effect profiles and can safely deliver ≥1000 mg of elemental iron in a single infusion.[26–28] Thus, they are better tolerated and more efficiently replenish iron stores than oral iron.[16,29–31] Studies to date have found that preoperative i.v. iron therapy modestly improves haemoglobin concentrations (by 5–10 g L^{-1}) and red blood cell (RBC) transfusion rates (by ~15%); however, a consistent corresponding effect on short-term *clinical outcomes* has not been observed.[32–37] The most recent systematic review (10 RCTs, n=1039) found that preoperative i.v. iron reduces RBC transfusions (relative risk [RR] 0.84; 95% confidence interval [CI] 0.71–0.99) but has no impact on morbidity and mortality (RR 0.96; 95% CI 0.78–1.65).[38] The costs of i.v. iron therapy are substantial (~450 CAD per 1000 mg dose plus administration costs), and as preoperative therapy is associated with reductions in transfusion but has not consistently been found to improve other important clinical outcomes, questions have been raised about its cost-effectiveness.[38–40] However, we believe that the problem is not with the use of i.v. iron therapy for treatment of surgical patients with iron-deficiency anaemia *per se*, but rather with the practice of limiting therapy to the preoperative period. Administration of preoperative i.v. iron is not possible for all patients owing to the requirement for an additional healthcare visit, need for outpatient i.v. infusion chair time, and need for third-party insurance for the costs for the product. Additionally, our study is unique in providing longitudinal follow up after surgery to patients, with additional doses of i.v. iron administered as indicated.

We hypothesise that in patients with chronic iron-deficiency anaemia undergoing cardiac surgery, i.v. iron therapy in the *postoperative* period will improve clinical outcomes, for three reasons. First, cardiac surgery exacerbates chronic anaemia and heightens physiological vulnerability to its complications, so treatment in this period may be particularly effective. Second, the postoperative hospital stay and subsequent follow-up appointments afford time to administer longer-term treatment (i.e. multiple i.v. iron treatments, if warranted) to achieve a sustained therapeutic response. Finally, postoperative i.v. iron therapy avoids preoperative treatment barriers such as a short lead time to surgery. Thus, we propose the POAM trial—an internal pilot RCT to establish the feasibility of a future, definitive RCT that will test the effect of postoperative i.v. iron therapy on clinical outcomes in patients with iron-deficiency anaemia who are undergoing cardiac surgery. The internal pilot design will use the data from the pilot study in the definitive trial, allowing efficient progression to a larger trial, should progression criteria be met.[41,42]

Methods

Aims and objectives

The overarching aim of this work is to assess the efficacy and safety of i.v. iron in cardiac surgical patients when used for the treatment of iron-deficiency anaemia in the immediate postoperative period and up to 6 weeks after surgery. The primary objective of this pilot study is to determine whether it is feasible to conduct a large, multicentre RCT testing the effect of longer-term (beyond index hospitalisation) postoperative i.v. iron therapy in patients with iron-deficiency anaemia undergoing cardiac surgery. The primary objective of the definitive study will be to determine, in patients with iron-deficiency anaemia undergoing cardiac surgery, whether i.v. iron therapy in the postoperative period (initiated shortly after surgery, and repeated at 6 weeks after surgery, if needed) improves clinical outcomes (days alive and out of hospital at 90 days after surgery [DAOH-90]) relative to placebo.

Study design and setting

The POAM study is a parallel-group, randomised, placebo-controlled, blinded, internal pilot clinical trial (Fig 1) of 60 patients conducted at three tertiary academic centres in Ontario,

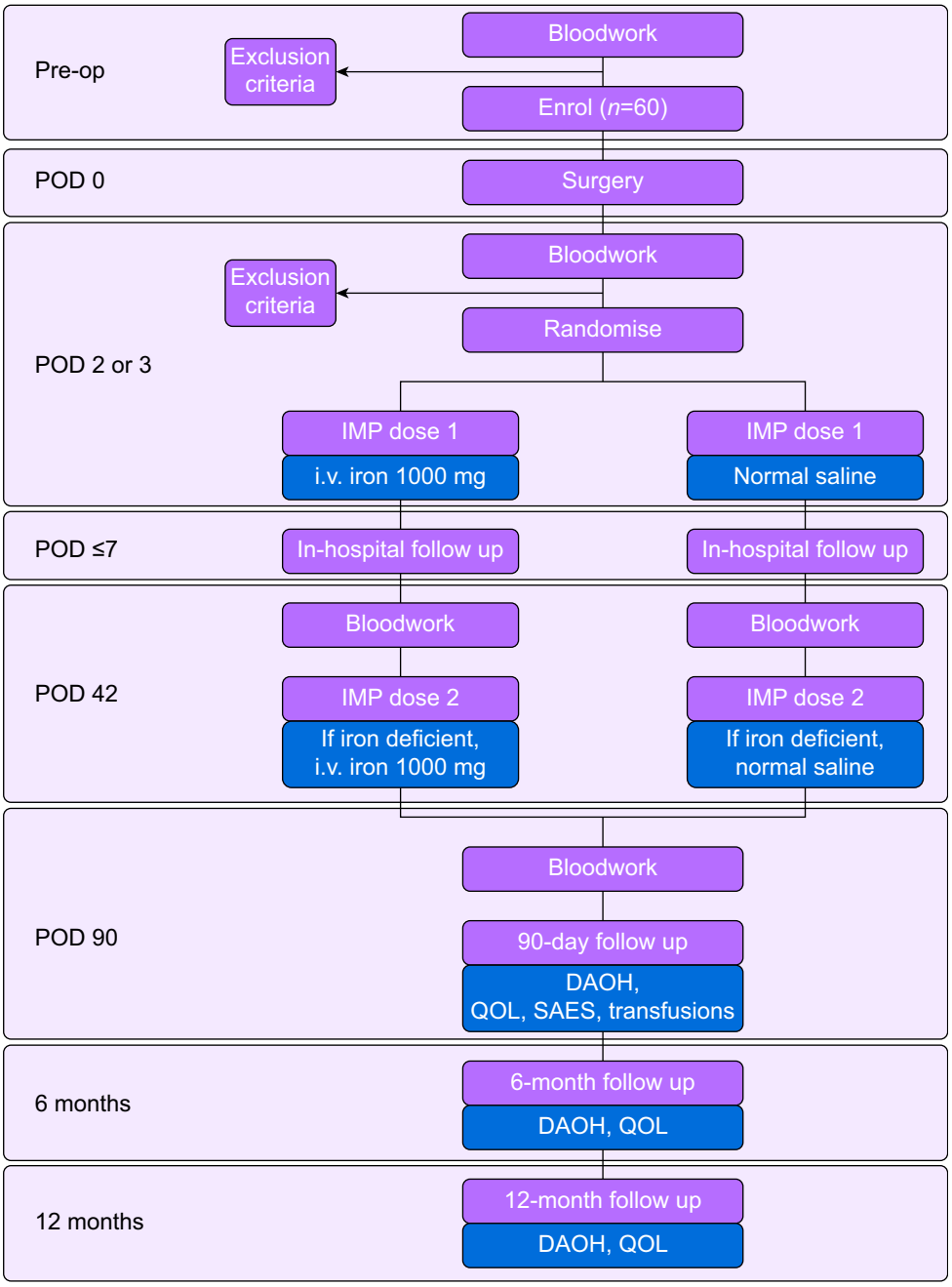

Fig. 1. Trial design. DAOH, days alive and out of hospital; IMP, investigational medicinal product; POD, postoperative day; QOL, quality of life; SAEs, serious adverse events.

Canada (Toronto General Hospital, Sunnybrook Health Sciences Centre, and Kingston Health Sciences Centre). Patients undergoing non-emergent cardiac surgery with iron-deficiency anaemia before surgery will be approached to enrol in the study (Table 1).

On postoperative day (POD) 2 or 3, patients will be randomised to receive either blinded i.v. iron (1000 mg ferric derisomaltose or if <50 kg an appropriate dose modification) or placebo, provided that they meet treatment criteria (Table 1). Six weeks after surgery, patients who remain iron deficient will receive a second blinded dose of i.v. iron according to their assigned treatment arm. Patients will be followed for 12 months. Clinical practice will not be otherwise modified. Pilot study feasibility will be assessed through rates of enrolment, protocol deviations, and loss to follow up.

This protocol adheres to the Standardized Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[44]

Table 1 Inclusion, exclusion, and randomisation criteria for participants in the POAM study. MELD, Model for End-Stage Liver Disease score.

Eligibility criteria (assessed at the time of surgical preadmission visit)

- Age >18 yr old
- Preoperative iron-deficiency anaemia, defined as a haemoglobin concentration <130 g L^{-1} with any one of:
  - o Ferritin <30 μg L^{-1}
  - o Ferritin 30–100 μg L^{-1} and transferrin saturation <20%
  - o Reticulocyte haemoglobin content <29 pg, where available[43]

Exclusion criteria

Patients who meet any of the following criteria are not eligible for the study:

- Specialised procedures (e.g. ventricular assist device insertion, thoracoabdominal aneurysm, complex adult congenital surgery, and heart transplant)
- Established contraindications to i.v. iron: o Hypersensitivity to the iron product
  - o History of two or more food, drug allergic reactions (excluding drug intolerances), or both
  - o Non-iron-deficiency anaemias such as myelodysplastic syndrome
  - o History of iron overload or disturbances in use of iron such as haemochromatosis or haemosiderosis
  - o Decompensated liver cirrhosis (MELD ≥19) or active hepatitis
  - o Active infection
- Preoperative unstable haemodynamics defined as the requirement for vasopressors or inotropes, or active bleeding (as noted in the clinical record and/or defined as a requirement for red blood cell transfusion for ongoing clinical bleeding)
- Refusal of blood products for religious or other reasons
- Known pregnancy
- Enrolment in another interventional trial, which may impact anaemia or transfusion management (e.g. a trial of haemostatic therapies, such as tranexamic acid)
- Receipt of i.v. iron at any point in the 6 weeks before randomisation

Treatment criteria for treatment (assessed on postoperative day 2 to 3)

- Stable haemodynamics (defined as no requirement for inotropes or vasopressors) and haemostasis without active bleeding (obtained from the chart and medical team, and defined as no clinically relevant bleeding resulting in ongoing transfusion requirements) or infections (vitals and bleeding information obtained from the chart and medical team)
- Presence of iron-deficiency anaemia, defined as a haemoglobin concentration <130 g L^{-1}, with any one of:
  - o Ferritin <100 μg L^{-1}
  - o Transferrin saturation <20%
  - o Reticulocyte haemoglobin content <29 pg, where available

Eligibility, exclusion, and treatment criteria

Adults (>18 yr) undergoing non-emergency cardiac surgery with cardiopulmonary bypass (CPB) will be eligible for inclusion in the study if they have iron-deficiency anaemia (see eligibility criteria in Table 1).[2,43,45–49] Patients for planned CPB were selected because of the larger volume of blood loss involved and higher probability of postoperative anaemia. We selected haemoglobin <130 g L^{-1} as the cut-off for iron-deficiency anaemia for both males and females because a lower cut-off of haemoglobin <120 g L^{-1} in females may contribute to worse outcomes, and this cut-off is now aligned with guidelines.[1–3,49,50]

Exclusion criteria are detailed in Table 1. We opted to exclude patients receiving i.v. iron in the 6 weeks before randomisation (~10% of anaemic cardiac surgery patients) as the therapeutic effect of i.v. iron plateaus 5 weeks after administration.[51] By excluding patients who have received i.v. iron but not achieved its full therapeutic effect, we prevent contaminating the treatment effect of postoperative i.v. iron with that of preoperative i.v. iron, which would bias our study towards the null hypothesis.

At POD 2 or 3, patients' haemoglobin and iron indices will be measured, and they will be randomised only if they meet treatment criteria (Table 1). Enrolled patients who do not meet these criteria will not be randomised, but will be followed to discharge.

Recruitment

Each participating study site has an active Patient Blood Management programme, which screens all patients undergoing elective cardiac surgery for iron-deficiency anaemia.[52] Before surgery, a research coordinator at each site will approach patients who meet the criteria for iron-deficiency anaemia to enrol in the study. Patients may be referred to the study team by the local Patient Blood Management coordinator or other members of the care team who have diagnosed anaemia. The research coordinator will provide study information and obtain informed consent in advance of surgery, and will confirm that inclusion and exclusion criteria are met. Given that anaemia is present in 30–40% of patients presenting for surgery,[2,5,6] we anticipate recruiting one to two patients per week from each institution.

Randomisation, allocation, and blinding

On POD 2 or 3, provided that treatment criteria are met, patients will be assigned to the intervention or control group according to a computer-generated randomisation scheme created by a biostatistician not involved in the trial. Allocation will use a 1:1 ratio, permuted blocks of varying sizes, and stratification (to ensure balanced groups) by site and preoperative anaemia treatment (no treatment *vs* treatment with oral iron or erythropoietin-stimulating agents). Once treatment eligibility has been confirmed, a research coordinator will use the randomisation module of REDCap to obtain an alphanumeric code for the patient, which will be emailed to the study pharmacist, who will prepare and blind the corresponding investigational medicinal product (IMP; i.v. iron or placebo) for that patient. A list indicating the treatment allocation that corresponds to each unique patient identifier will

be maintained in the research pharmacy of the participating sites. Patients, clinicians, and all study personnel (including outcome assessors) will be blinded to group allocation. As the IMPs have different physical properties, an unblinded pharmacist will blind the IMP by placing an opaque cover on the i.v. bags and opaque tape on the i.v. tubing, or opaque tubing. Pharmacists will not have access to study data.

Intervention and control

Patients randomised to i.v. iron will receive 1000 mg ferric derisomaltose (Monoferric; Pfizer[53]) diluted in 100 ml of normal saline (NS), over 1 h via an opaque i.v. bag and tubing. An appropriate dose adjustment will be provided for patients <50 kg. Guidelines recommend at least 1000 mg of i.v. iron to replete stores[54–56] as iron-deficiency anaemia occurs when essentially all iron stores have been depleted. Those randomised to placebo will receive 100 ml of NS via identical opaque i.v. bag and tubing. This first dose of IMP will be prepared by the research pharmacy and administered by a bedside nurse (as per current standard of care) on POD 2 or 3, when haemostasis and haemodynamics after surgery have stabilised. To avoid unnecessary iron treatment, iron-deficiency anaemia will be confirmed as noted in the treatment criteria (Table 1).

At 6 weeks (POD 42 [SD 7 days]) after surgery, all patients will have a follow-up visit (which we will align with the routine in-person surgical follow up, whenever possible). Patients will have their haemoglobin and iron indices measured before or during the visit (at an external laboratory for patient convenience or at the hospital). Based on results, patients who remain iron deficient and have no contraindications for i.v. iron therapy (Table 1)[48,57] will receive a second blinded dose of IMP according to their assigned treatment arm. Patients who are not iron deficient will not receive an infusion. This will not compromise blinding as a certain proportion in each study arm (although less in the i.v. iron arm) will not require IMP dose 2.

Outcomes

Table 2 indicates the timing and frequency of data that will be collected during the study. Patients will be followed up at POD 7 (or discharge, if earlier), POD 42, POD 90, and 6 and 12 months after surgery (Fig 1).

The outcomes of the pilot study for assessing the feasibility of the definitive study are as follows, with feasibility targets in parentheses: percentage of major protocol deviations (i.e. treatment not according to randomisation allocation or dosing schedule; treatment initiated in ineligible patients; <5%); adequate patient enrolment (>20% of eligible patients

Table 2 Flow chart of assessments performed throughout the study. AEs, adverse events; CPB, cardiopulmonary bypass; DAOH, days alive and out of hospital; DC, discharge; POD, postoperative day; SAEs, serious adverse events; (x) if needed.

Procedures	Visit 1 Before surgery	Visit 2 POD 2 or 3	Visit 3 PODs 2–7/DC	Visit 4 POD 42	Visit 5 POD 90	Visit 6 6 months	Visit 7 12 months
Obtain consent	x						
Eligibility criteria	x						
Treatment criteria		x		x			
Randomisation		x					
Interventions administered		x		x			
Baseline data							
Patient characteristics	x						
Medical history	x						
Concomitant medications	x	x	x	x	x	x	x
Surgical data							
Procedure details	x	x					
Intraoperative medications		x					
CPB time		x					
Cross-clamp time		x					
Circulatory arrest		x					
Fluid input and output monitoring		x					
Inotropes and vasopressors		x					
Laboratory assessments							
Chemistry	x	x	x	x	x		
Haematology	x	x	x	x	x		
Coagulation profile	x						
Safety labs	x	x	x	x	x		
Additional endpoints							
DAOH					x	x	x
Hospital length of stay			x	(x)	(x)	(x)	(x)
Alternate Care Facility length of stay			x	(x)	(x)	(x)	(x)
Transfusion requirements		x	x		(x)		
Quality of life	x			x	x	x	x
Safety endpoints							
AEs and SAEs		x	x	x	x	x	x
Treatment-emergent events		x	x	x	x	x	x
Duration of ICU stay		x	(x)	(x)	(x)	(x)	(x)
All-cause mortality					x	x	x

enrolled); and percentage of patients lost to follow up at 90 days (<5%).

Based on the result for each primary feasibility outcome, we will determine whether the definitive study is feasible as proposed (all feasibility endpoints are met), feasible with protocol modifications, or not feasible because feasibility targets could not be met even with protocol modifications.[41] To decide if major protocol deviations exceed our feasibility target, we will hold an investigator meeting to examine the type and number of major deviations[58–60] and whether protocol modifications are needed.

Secondary feasibility outcomes are: percentage of patients in the placebo arm receiving i.v. iron between randomisation and POD 90 (i.e. crossover events; ≤10%); differences in the distribution of patients and clinicians correctly guessing treatment allocation between the i.v. iron and placebo groups (i.e. inadvertent unblinding); percentage of patients lost to follow up at 6 and 12 months (<5%); and proportion of missing case-based costing data.

We will also collect the outcomes that we intend to use for the definitive study, which will be examined for rates of missing data and the quality of data captured. Results will not be examined by treatment arm because, owing to the nature of the internal pilot study, results will remain blinded to investigators and participants until completion of the definitive study.

The planned primary efficacy outcome for the definitive study will be the DAOH-90.[61] To calculate DAOH-90, patients who die during the 90-day period are assigned a value of 0; otherwise, patients are assigned the number of days they spend outside of the hospital in the 90 days after surgery. DAOH is highly sensitive to changes in surgical risk and complications.[62–64] It is an objective, patient-centred measure that does not need adjudication and is easy to interpret.[65]

Secondary efficacy outcomes are: days alive and at home (i.e. outside of hospital, rehabilitation, respite, and chronic care settings) in the 90 days, 6 months, and 12 months after surgery; change in quality of life (Eq-5D-5L,[66–68] FACIT-Fatigue Scale[69]) from baseline to 42-day, 90-day, 6-month, and 12-month follow up; number of units of allogeneic blood components administered from randomisation to POD 90; change in haemoglobin and iron indices from baseline and randomisation to discharge, POD 42 and POD 90; incidence of thromboembolic and infectious events, treatment-emergent serious adverse events (SAEs; e.g. thromboembolic and infectious events, infusion-related reactions, and reactions specific to i.v. iron), and mortality; all hospital and emergency department visits; and resource use and cost.

Sample size

The sample size of 60 patients allows for sufficiently precise estimates of feasibility outcomes[70] in a reasonable timeline. Percentages meeting or exceeding 20% feasibility target where higher percentages are desirable (e.g. enrolment rate) will have a lower one-sided 95% confidence limit of 10% or more. Percentages meeting or decreasing below 5% feasibility targets where lower percentages are desirable (e.g. loss to follow up) will have an upper one-sided 95% confidence limit of 12% or less. The size of the definitive trial is yet to be confirmed, as it requires data from the pilot study on the distribution of DAOH-90 and a judgement on the difference in DAOH that would be needed to justify the cost of routine postoperative i.v. iron therapy in this patient group. We have made approximate calculations based on available institutional data. Monte Carlo simulation finds that a trial of 800 patients per group, analysed with the Wilcoxon rank sum test has 90% power (at a 5% type I error rate) if there is a 1-day difference in DAOH. For a 2-day difference, the sample size is approximately 200 per group. Patients enrolled in the pilot study will be included in the definitive trial if no design changes are needed.

Data collection and management

Study data will be collected using REDCap. Standardised case report forms will be created in REDCap for collecting outcome data, with real-time checks for validity and completeness. The site investigator will maintain a confidential list of patient identification codes, source records, and source data, which will be preserved according to regulatory authorities. Patient data will be kept confidential and will only be accessible by delegated personnel.

Statistical methods

In the pilot study, we will estimate rates and percentages for feasibility outcomes, along with lower one-sided 95% CIs where high percentages are desirable (e.g. enrolment rate) and upper one-sided CIs where low percentages are desirable (e.g. loss to follow up, protocol deviations). Point estimates will be compared with the feasibility targets to make decisions on feasibility and the need for changes to the protocol. At the end of the pilot study, the sample size for the definitive trial will be recalculated based on information obtained from the internal pilot. In the pilot study, no subgroup analyses will be performed. The full analysis plan for the definitive trial is planned to be detailed in its own published protocol, along with accompanying economic analyses.

Monitoring and quality control and assurance

The trial will be coordinated by the Anesthesia Clinical Trials Unit (ACTU) at University Health Network (UHN), which has conducted several large RCTs.[71–73] A steering committee with diverse clinical and methodological expertise will be the governing body and will meet monthly to review progress and operational issues, including whether to continue. An independent data safety and monitoring committee (IDSMC) will have expertise in cardiac surgery, transfusion medicine, and clinical trial methodology/statistics. Every 30 randomised patients or as required based on treatment-emergent SAEs, the IDSMC will review unblinded summary statistics for safety, endpoints, and other study data (e.g. enrolment, retention, compliance, data quality, and timeliness) to identify problems and assess the assumptions made at study start. Only if the IDSMC identifies issues will they advise the principal investigator in a non-treatment-disclosing manner on the problems. The IDSMC will advise the steering committee on medical questions and issues of study conduct and continuation. The IDSMC will be independent of the investigating team in operating and formulating recommendations. Unless advised otherwise, the study will continue until follow up is complete for 60 enrolled patients.

An independent study monitor will be given direct access to source documents to periodically review all study-related source data and records, verify the adherence to the protocol

and the completeness, correctness, and accuracy of all case report form entries compared with source data.

Anticipated challenges

As much as possible, this study uses a pragmatic approach for clinical management to allow the clinical care teams to maintain standard practices. Preoperative care will not be altered but will be accounted for with stratified randomisation and analysis. Perioperative care will also not be altered. Patients who have received or will receive i.v. iron within 6 weeks before surgery will be excluded. In all other patients, aside from IMP administration, preoperative and postoperative management will be unchanged. We will allow preoperative erythropoietin-stimulating agents and oral iron at any time, which we will account for with stratified randomisation and subgroup analyses. We do not anticipate concomitant oral iron therapy will be a concern as preoperative oral iron is not beneficial,[74–77] and postoperative oral iron therapy is ineffective, has poor compliance, and is not commonly prescribed.[78,79]

Because anaemia and RBC transfusion are highly interrelated,[80] information on transfusion of blood components and all haemostatic agents will be collected. Postoperative transfusion will be according to a standardised institutional transfusion algorithm and according to guidelines.[81–83] Any patient who remains moderately anaemic (haemoglobin $\leq$110 g L^{-1}) at POD 90 will be referred to their primary care provider for follow up and treatment.

We anticipate minimal loss to follow up as cardiac surgery patients are followed closely by surgeons and cardiologists after surgery. A recent systematic review found minimal loss to follow up in major cardiovascular clinical trials, even with extended follow up (median 2%, inter-quartile range 0.3–5.3%).[84] To address barriers that may cause patients to drop out of the study, we will limit trips to the hospital by allowing follow-up blood tests to be done at local laboratories and conduct the 90-day, 6-month, and 12-month follow up virtually. To address financial barriers, we will reimburse patients for each follow-up blood draw.

Determination of feasibility

Based on the result for the feasibility outcomes, we will determine whether the definitive study is feasible as proposed (the feasibility endpoint is met with the current protocol), feasible with modifications to the protocol to address feasibility outcome, or not feasible because the feasibility target is not met or could not be met even with modifications to the protocol.[41,85] To make this decision, if the percentage of major protocol deviations exceeds our feasibility target of 5%, an investigator meeting will be held where the type and number major deviations will be examined and classified according to whether it is related to the protocol and referenced documents or if an event occurred that was independent of blame (i.e. sample tube broken *en route* to the laboratory). The frameworks developed by the Drug Information Association and TransCelerate BioPharma for managing major protocol deviations[58] will be utilised. For inadequate patient enrolment, attempts will be made to improve study procedures (i.e. amendments to protocol, education and training of study personnel, or better engagement with sites and other stakeholders). We will also assess the total number of patients excluded and the specific reasons for exclusion to understand potential modifications required in our enrolment criteria.

Ethics and dissemination

The trial will be conducted in accordance with the Declaration of Helsinki[86] and Good Clinical Practices guidelines,[87] and the study protocol, which has been approved by research ethics boards from the University Health Network (REB # 22-5685; approved on 22 December 2023 by Clinical Trials Ontario), and the regulatory authority (Health Canada). The trial is registered at clinicaltrials.gov (NCT06287619). Changes to the protocol will be communicated to each investigator, Research Ethics Board, Health Canada and registered on clinicaltrials.gov. No study interventions will occur before written consent. Randomising patients to i.v. iron or placebo after surgery is not expected to pose significant risks.[88] Patients are completely free to withdraw from the study at any time, without any consequences for their further care, and that his/her medical records may be reviewed in accordance with applicable regulations.

Authors' contributions

Study design: JB, SM, ML, JC, SAM, YL, KK.
Writing protocol: JB, SM, JC, SAML, YL, KK.
Drafting the article: JB, SM, SA, DG, JC, SAM, YL, KK.
Critical revision of the article: JB, SM, SA, DG, JC, SAM, YL, KK.

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Declarations of interest

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