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Active **P**reoperative **A**nemia Management to **R**educe Erythrocyte **T**ransfusion in Patients undergoing Cardiac Surgery (APART): A Feasibility Propensity-Matched Study

UT Southwestern
Department of Anesthesiology
And Pain Management

Principal Investigator: Philip E. Greilich, M.D.

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I. INTRODUCTION AND PURPOSE:

Every year, over 600,000 open-heart operations are performed in the United States alone. Preoperative anemia is highly prevalent in this population of patients. A recent study involving over 4,800 patients undergoing coronary artery bypass grafting (CABG) at 70 institutions worldwide revealed that greater than 30% of patients fulfilled the World Health Organization criteria for anemia in the preoperative period.[1] A recent review of this topic reported that preoperative anemia may exceed 50% in some institutions.[2] This is particularly concerning given that several large risk-adjusted, retrospective and observational studies have demonstrated that preoperative anemia is associated with a two-fold increase in morbidity and mortality in this patient population[1,3,4-5] The vast majority of patients undergoing cardiac surgery require cardiopulmonary bypass (CPB). The average drop in hemoglobin concentration (from preoperative levels to nadir) in these patients is between 4-6g/dL.[51] Preoperative anemia, combined with significant, acute blood loss (750mls - 2,000mLs) and the hemodilution (30-40%) associated with CPB frequently leads to hemoglobin levels that result in insufficient oxygen delivery (DO2) and organ dysfunction.[3,6-7]

Anemia and transfusion are independent predictors of morbidity and mortality in this patient population. Preoperative anemia is the single most important predictor of perioperative erythrocyte transfusion.[8] Karkouti et al. demonstrated that approximately 80% of patients with preoperative anemia received at least one erythrocyte transfusions while undergoing cardiac surgery.[3] While open cardiac surgeries represent only 1% of the 48 million in-patient surgeries performed annually in the U.S., this small population of patients consumes over 20% of the red blood cell supply in U.S. blood banks.[3,9] Of those transfused, over 50% receive $\leq$3 units of red blood cells.[10] Whereas transmission of infectious disease has been a historic concern, we now realize that adverse outcomes are more commonly the result of immunomodulation, hypoxia, and free radical induced injury.[11,12] Studies have repeatedly demonstrated that even low-volume erythrocyte transfusions (1-3 units) can significantly increase the risk of acute renal injury, infection, and pulmonary dysfunction following cardiac surgery.[1-3,8,9] Reduction and possible elimination of RBC transfusion is now recognized as one of the most significant *modifiable* risk factors leading to these adverse events.

The mechanism of injury in patients with preoperative anemia is either the duration/intensity of the anemia exposure (and resultant organ ischemia) or the harmful effects of erythrocyte transfusion(s) itself. Active preoperative anemia management is a strategy that attempts to minimize both of these events, and in doing so, exert an additive or possibly synergistic effect on improving clinical outcomes. A randomized controlled trial utilizing a standardized transfusion strategy is sorely needed to determine if increases in preoperative hemoglobin lead to improved outcomes. Conducting a feasibility propensity-matched study is an essential step for insuring the adequacy of future trials designed to answer this important question.

The use of erythropoietin (EPO) is one method for optimizing hematopoiesis especially in those with preoperative anemia. In fact, evidence-based practice guidelines currently recommend selective, short-term, preoperative use of EPO plus supplemental iron to optimize erythropoiesis and to reduce erythrocyte transfusions in the perioperative setting.[13-15] The "Blood Conservation in Cardiac Surgery" guideline, updated in 2011, states "it is reasonable to use preoperative EPO plus iron, given several days before cardiac operation, to increase red cell mass in patients with preoperative anemia (AHA class IIA recommendation; level of evidence B)".[14] This recommendation is based on six randomized trials (810 subjects) that used an *ultra*-short course of EPO (<5 days) in patients scheduled for cardiac surgery. Wide adoption of these recommendations has been, however, very slow. Significant limitations in previous work include:

1) insufficient treatment duration/dosing to increase red blood cell mass enough to avoid more than 1U of red blood cells[15-18];
2) widely variable and inadequate dosing (dose, frequency, route of administration) of supplemental iron for an optimal erythrocytic response; and
3) a need for a simple and safe method to administer and monitor EPO plus iron in anemic patients scheduled for cardiac surgery.

We therefore propose a feasibility propensity-matched study to test the safety and efficacy of using a short- course (1-4 weeks) of EPO plus intravenous (IV) iron to increase erythrocyte mass. The findings from this study will be used to design a phase II/III randomized, controlled trial to determine if a similar treatment (EPO + IV iron) can significantly reduce erythrocyte transfusion and postoperative complications in anemic patients undergoing cardiac surgery.

Aims in this pilot feasibility study are as follows:

- *Specific Aim 1:* Among patients scheduled to undergoing elective coronary artery bypass graft surgery (CABG), valve repair or replacement surgery (valve), or CABG/valve at UTSW University Hospital, to determine the proportion of patients who fulfill all the eligibility criteria for the study and agree to be part of a propensity-matched study of short-course EPO (up to 3 doses given over a 1-4 week interval prior to surgery and a postoperative dose 2-4 days following surgery) plus supplemental IV iron (2 doses) vs. untreated matched patients scheduled for CABG, valve, or CABG/valve surgery.

- *Specific Aim 2:* To determine the adherence of patients and health care team to the procedures included in the study protocol (scheduled appointments, surveillance and transfusion strategies).

- *Specific Aim 3*: To determine the increase in hemoglobin levels and reticulocyte count following a

short-course of EPO plus supplemental IV iron vs. standard of care management in matched patients scheduled for CABG, valve, or CABG/valve surgery.

- *Specific Aim 4:* To assess differences in the proportion of patients receiving erythrocyte transfusions and number of blood products utilized (RBC, platelets and plasma) in the peri- and post-operative periods for those receiving a short-course of EPO plus supplemental IV iron vs. standard of care management in matched patients scheduled for CABG, valve, or CABG/valve surgery.

- *Specific Aim 5:* To determine the frequency and intensity of pre-defined clinical outcomes (mortality, major cardiac, renal, neurological events [associated with anemia] and infection) in those receiving a short-course of EPO plus supplemental IV iron vs. standard of care management in matched patients scheduled for CABG, valve, or CABG/valve surgery.

II. BACKGROUND:

Active preoperative anemia management is *not* currently the standard of care at our institution. Cost associated with erythrocyte transfusions at UT Southwestern University Hospitals exceeds $20M dollars annually. This figure does not include costs associated with treatment of known complications of red blood cells transfusions (renal insufficiency, respiratory failure, infection and prolonged length of stay, etc).[19-20] Fifty percent (50%) of our cardiac surgical population suffers from preoperative anemia and seventy-nine (79%) of these patients will receive one or more erythrocyte transfusions. In contrast, the incidence of erythrocyte transfusion was only 35% in those *without* preoperative anemia in CY2011-12.

The goal of active preoperative anemia management is to restore red blood cell mass and reduce complications associated with anemia and erythrocyte transfusion. The use of erythrocyte stimulating agents (ESAs) has been effective in increasing hemoglobin levels and reducing red blood cell transfusion requirements in a variety of settings. Although commonly used to treat anemia in patients with chronic renal failure and certain types of cancers, short-term pre- and peri-operative use of EPO is one strategy for addressing the high prevalence of anemia (20%-50%) in the aging surgical population. The safety and efficacy of recombinant human EPO use in orthopedic[21-23] and gynecological surgeries[24-25] are well-documented. Dosing and duration have generally been EPO 600U/kg once weekly for a total of four weeks. No differences in the incidence of adverse events have been demonstrated between the treatment and control groups in these studies.

Six randomized controlled trials have been published using EPO in the setting of cardiac surgery.[15-18,21,26] Those receiving EPO demonstrated a greater increase in hemoglobin concentration on the day of surgery (1.4g/dL - 2.1g/dL; compared to baseline; $p < 0.05$)[17-18] with fewer erythrocyte transfusions (1U vs. 2U; *p*

< 0.01) compared to placebo controls.[18] These regimens were *ultra*-short in duration (≤5 days) and in some studies included a postoperative dose.[15,17,26] No differences in adverse events were noted in the 810 subjects enrolled in these studies. However, none of these studies were sufficiently powered to detect either differences in clinical outcome or safety. As such, the beneficial effects of an *ultra*-short course of EPO remain uncertain. Studies from the orthopedic surgery literature suggest that longer treatment intervals will likely be required to increase red blood cell mass to a level capable of reducing erythrocyte transfusions to the degree needed to detect an independent effect on clinical outcome. Prolonged use of these agents (EPO, darbepoetin) in patients with cardiovascular disease and heart failure have been shown to be safe.[27,28] The Study of Anemia in Heart Failure Trial (STAMINA-HeFT), the largest of these multicenter, randomized, controlled trials, demonstrated that darbepoetin was effective in raising the hemoglobin levels (1.8g/dL vs. 0.3g/dL; p<0.001) without increasing the risk of ischemic complications.[28] In fact, a trend towards lowering the risk of morbidity and mortality was observed in the 162 subjects enrolled in the treatment group.

Overuse of EPO in patients undergoing cardiac surgery needs to be monitored. A study by D'Ambra et al.[15] demonstrated that aggressive dosing of this agent in *non*-anemic patients could be problematic. Given its potential to contribute to a pro-thrombotic phenotype in some individuals, even its short-term use in patients with unstable angina is discouraged by the cardiac surgery practice guidelines.[14] Its black box warning for chronic use in patients with end stage renal disease with cardiovascular disease is also intended to minimize the risk of a thrombotic event. The package insert for darbepoetin also recommends holding scheduled doses should the rise in hemoglobin level exceed 1g/dL per week based on an anaylsis of their safety data.[29-30] The creation of a surveillance strategy is one method to increase the safety of EPO use by monitoring patient characteristics that may present an increased risk of a thrombotic event in this clinical setting. This strategy could include:

1) limit use to those with preoperative anemia;
2) hold scheduled doses in those with hemoglobin thresholds deemed to be safe;
3) limit the duration of treatment or total number of doses;
4) administer treatments in close proximity to the scheduled surgical date; and
5) hold post-operative doses in patients with laboratory evidence of a hypercoagulable state.

Iron is an essential co-factor for erythropoiesis. Absolute or functional iron deficiency is a common reason for an inadequate erythropoietic response to acute anemia and EPO therapy. Intravenous iron administration is the most reliable method for insuring this vital co-factor is not the rate-limiting step in restoring red cell mass with EPO.[4,15] Although iron supplementation *alone* has been effective in restoring red blood cell mass and decreasing erythrocyte transfusion in *non*-cardiac surgery,[4] this finding has *not* been demonstrated in cardiac surgery where blood loss is generally higher.[31]

Randomized controlled trials designed to test the hypothesis that active preoperative anemia management improves clinical outcomes have been called for by numerous large, observational trials, but to date have not been performed. This feasibilitypropensity-matched study builds upon the safety record that *ultra*-short duration (≤5 days) EPO use in cardiac surgery by extending the duration of treatment to 1-4 weeks and including supplemental IV iron in the treatment group. The design of this study includes transfusion and surveillance strategies to minimize the confounding influence of overuse of either erythrocyte transfusions and/or EPO on clinical outcomes.

III. CONCISE SUMMARY OF PROJECT

Research Design and Methods:

Propensity score matching (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment or other intervention by accounting for the covariates that predict receiving the treatment. PSM attempts to reduce the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcomes among units that received the treatment versus those that did not. This feasibility propensity-matched study is being conducted to guide the design of a future randomized, controlled trial (RCT) that examines the effects of active preoperative anemia management on erythrocyte transfusion and clinical outcomes. The RCT will test the hypothesis that a *short*-course (1-4 weeks) of EPO plus IV iron is superior to the standard of care at reducing erythrocyte transfusion and improving outcomes in *anemic* patients scheduled for cardiac surgery. Means and standard deviations derived from pilot data on changes in hemoglobin levels, reticulocyte count and differences in erythrocyte transfusion and clinical outcomes will be analyzed for possible use in sample size calculations for the larger RCT. This study will also provide valuable information in determining whether the addition of other clinical sites with similar patient populations will be needed in order to help recruit patients for timely completion of the RCT. In addition, the study will provide important information on issues related to data collection, data management, adherence to the study protocol, transfusion and surveillance strategies and classification of clinical outcomes and adverse events.

Anemic patients scheduled to undergo CABG, valve, or CABG/valve surgeries will be considered for the study. Patients who fulfill all the inclusion/exclusion criteria will be asked to participate in the study. The proportion of screen failures and eligible patients who refuse to participate will be recorded using a screen failure log. Patients who agree to be in the study and sign an informed consent form will be sequentially enrolled into the treatment group. The treatment group will receive up to three doses of EPO 300U/kg. The first dose of study medication will be administered up to 28 days before the day of surgery and the second will be administered 1-7 days before the day of surgery. These first two doses will be given at least 7 days apart. A third dose may be administered two to four days following surgery. All 3 doses will be administered subcutaneously and per surveillance strategy guidelines. In addition, supplementation

with IV iron (feraheme; 510mg delivered per IV infusion over a minimum of 15 minutes) will be given following the first two preoperative doses of EPO.

Differences in hemoglobin levels and reticulocyte counts from baseline to the day of surgery (preop to POD#0) and postoperative day five (POD#5), proportion of patients receiving erythrocyte transfusions and number of blood products (RBC, platelets and plasma) utilized and pre-defined clinical events (mortality, major cardiac, renal, neurological events [associated with anemia] and infection) will be assessed in all treated participants. Each patient will be enrolled in the study up to 28 days before the day of surgery and for up to 30 days following the day of surgery. This feasibility propensity-matched study will sequentially enroll 23 more treatment subjects to total 25. The propensity-matching control group will be comprised of 25 total "like" patients for comparison. The source of the data for the control group will be the Society of Thoracic Surgery (STS) Database, an institutional registry.

Study medications:

1. EPO (Procrit®; Janssen Biotech, Inc; Horsham, PA) is a medication that promotes erythropoiesis and is indicated for the reduction of allogeneic erythrocyte transfusions in patients undergoing elective noncardiac, nonvascular surgery.[29, 30, 32] Native EPO is a 165 amino acid glycoprotein hormone that binds to the EPO receptor on erythroid progenitor cells to induce intracellular signaling that inhibits apoptosis important to erythroid differentiation. EPO differs only slightly (protein moiety) from its native form. EPO may be administered intravenously, intraperitoneally or subcutaneously. Subcutaneous administration results in peak concentrations at about 18 hours. The bioavailability of subcutaneous EPO is about 20 to 30% and detectable serum concentrations are still present 4 days after administration. Remarkably, little is known of the mechanism in which either endogenous EPO or recombinant human EPO is metabolized. About 3 to 10% of EPO is excreted unchanged in the urine. In common with other glycoproteins, the carbohydrate residues which constitute 40% of its molecular size are essential for maintaining the stability of EPO in circulation. The most common serious adverse effects are hypertension, bleeding and thrombotic events. Caution is advised with chronic (over 2-3 months) administration in patients who are at high risk for thromboembolic events. Relatively short-duration (<1 month) administration, however, has demonstrated a promising safety profile.[16-18] No significant differences in adverse events related to EPO administration have been reported in the literature for over fifteen years.[16-18,21]

2. Intravenous Iron supplement (Feraheme™ AMAG Pharmaceuticals, Inc, MA): Feraheme injection is an IV iron indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.[33] Feraheme consists of a super-paramagnetic iron oxide coated with a carbohydrate shell, which helps to isolate the bioactive iron from plasma components. The iron is

released within vesicles in the macrophages of the reticuloendothelial system, and the iron subsequently enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin. Feraheme exhibits a dose-dependent elimination from plasma with a half-life of approximately 15 hours in humans. The clearance decreases by increasing the dose of feraheme. Volume of distribution is consistent with plasma volume, and the mean maximum observed plasma concentration and half-life increases with dose.

Transfusion Strategy:

Retrospective analyses in cardiac surgery demonstrate increased morbidity and mortality with intraoperative hemoglobin between 5.0g/dL to 8.0g/dL (Hct 15-24%) and postoperative hemoglobin >11g/dL (Hct >34%).[6,12,14,34] In addition, two recent RCT[35-36] demonstrated no clear advantage of using a transfusion threshold >8g/dL unless patients are experiencing symptoms of anemia, rapid blood loss or life-threatening circulatory shock. Lower transfusion threshold appears justified during CPB because metabolic demands are reduced during anesthesia and CPB. Hematocrits as low as 22% during CPB have been shown to be well-tolerated.[37-38] In fact, transfusing patients with hematocrits >22% during CPB have been associated with increases in adverse events (especially in low- and moderate-risk sub-groups).[34,39]

A consensus for transfusion thresholds was established among anesthesiologists, perfusionists and surgeons in our practice. The transfusion thresholds implemented in this protocol reflects our current "standard of care;" a threshold at which clinicians generally believe the benefits of erythrocyte transfusion outweigh the risks. Adherence to the transfusion strategy will be recorded by the research nurse and protocol deviations will be discussed with the attending physician of record and a member of the clinical research team. However, research staff will not order nor prohibit erythrocyte transfusions. This will be left to the discretion of the treating physician(s) if he/she deems it clinically necessary. Following randomization, patient's charts will be clearly labeled to indicate participation in the study protocol.

Erythrocyte transfusion is permitted during CPB if:

- Hemoglobin <6.0g/dL;
- Hemoglobin between 6.0g/dL and 8.0g/dL if the patient
  - is considered high-risk by:
    - ✓ EuroScore or Higgins Score ≥6 and ≥10, respectively
    - ✓ age >75yrs
    - ✓ history of stroke or TIA or baseline cognitive dysfunction or dementia
    - ✓ incomplete revascularization
  - demonstrates signs of inadequate organ perfusion despite MAP ≥60mmHg or CPB flows of ≥2.5L/kg/m^2 evidenced by

- ✓ myocardial ischemia (by EKG or TEE) despite an adequate MAP
- ✓ mixed venous oxygen saturation (Sv02) <60%

➢ unable to separate from CPB despite adequate doses of inotropic/pressor support

Erythrocyte transfusion is permitted intra- and post-operatively if:

- Hemoglobin <8.0g/dL
- Hemoglobin between 8.0g/dL and 9.5g/dL, if the patient
  - ➢ is experiencing rapid blood loss (≥300mLs/hr)
  - ➢ is experiencing signs/symptoms of anemia evidence by
    - ✓ tachycardia and/or hypotension (MAP <60mHg for >10mins) unresponsive to adequate volume replacement alone
    - ✓ escalating doses of 2 or more inotropic / pressor agents (i.e. EPI/NE ≥0.03 mcg/kg/min)
  - ➢ is experiencing signs/symptoms of inadequate oxygen delivery or circulatory shock
    - ✓ cardiac index <2.0L/min/m^2
    - ✓ mixed venous/central venous oxygen saturation (Sv02)/Scv02) ≤60%
    - ✓ base deficit >6.0mEq/L in absence of renal failure
    - ✓ urine output <0.5mL/kg/hr
  - ➢ is considered high-risk by EuroScore or Higgins Score (≥6 and ≥10, respectively)
- If the patient does not demonstrate any of the signs/symptoms above, yet the physician still believes an erythrocyte transfusion is warranted, he/she will be asked to provide a justification that will be recorded and classified.

Erythrocyte transfusions should be given <u>one</u> unit at a time with measurement of the pre- and post-transfusion hemoglobin levels along with physiologic parameters used to assess adequacy of organ perfusion.

<u>Surveillance Strategy for ESA Dosing:</u>

The decision to initiate and continue administering doses of EPO is based on evidence accrued from randomized controlled trials and clinical practice guidelines provided by multiple sub-specialty and international societies.[14,40-41] Substantial heterogeneity exists in factors that could be included in a surveillance strategy to minimize the risk of a thrombotic event in this setting; with no one strategy proven to be superior. The surveillance strategy included in this protocol derives from, what we believe to be, the most current safety analyses of perioperative EPO use reflected in the literature. Implementing such surveillance methods are intended to minimize the possibly rare but potentially life-threatening adverse events. Risk factors considered in our surveillance strategy include: evidence of unstable angina or myocardial infarction, recent thrombotic event, hemoglobin levels associated with a higher risk of a

myocardial event, excessive thrombocytosis (platelet count >300 x10^3/μL) or laboratory evidence of a hypercoagulable postoperative state.

EPO dosing will be stratified based on patient risk (degree of perioperative anemia), type of procedure (CABG vs. valve) and laboratory data (Hb, RoTEM: MCF) in the following manner:

Initial dosing/Re-dosing of EPO plus IV iron (Prior to Surgical Procedure):

Therapy or a dose will **NOT** be administered in patients under the following conditions:

- Patients scheduled for a CABG procedure with Hb concentration ≥12.5g/dL
- Patients scheduled for a cardiac valve procedure with Hb concentrations ≥13.5g/dL
- Rate of rise in Hb level that exceeds 1g/dL in past 7 days (and not secondary to erythrocyte transfusion)[a]
- Evidence of any new or evolving symptoms or signs suggesting the presence of myocardial ischemia, including chest pain, EKG changes, or elevation of laboratory cardiac biochemical (CK-MB, Troponin)
- Average of three diastolic blood pressures (over 1hr) >100mmHg despite scheduled anti-hypertensive therapy.

[a] **Rationale:** The original label for EPO[29-30] included a warning regarding the risk of exacerbation of hypertension with hematocrit increases exceeding 4 percentage points (corresponding to increases in the hemoglobin concentration of approximately 1.3 g per deciliter) within a 2-week period. During a review of the marketing application, an association was found between rates of increase in the hemoglobin level exceeding 1g/dL per 2-week period and the risk of cardiovascular and thromboembolic events. This observation provided the basis for a warning on the package insert for darbepoetin regarding excessive rates of increase in hemoglobin concentrations.

Continuation of Dosing of EPO (Post-Operative Administration)

Postoperative therapy will **NOT** be administered in patients under the following conditions:

- Hb concentration >10.0g/dL (both CABG and valve procedures) [b]
- Rotational Thromboelastogram (RoTEM) measurement of Maximum Clot Firmness (MCF) >70mm (RoTEM to be performed during procedure and 2-4 days after surgery, prior to re-dosing).
- Evidence of any new or evolving symptoms or signs suggesting the presence of myocardial ischemia, including chest pain, EKG changes, or elevation of laboratory cardiac biomarkers (CK-MB, Troponin) that have failed to have a decreasing trend
- Average of three diastolic blood pressures (over 1hr) >100mmHg despite scheduled anti-hypertensive therapy.

[b] **Rationale:** A multi-center study in over 2,000 CABG patients by Spiess et al.[12] demonstrated that hematocrit >34% (11.3g/dL) upon entry in the ICU was the single greatest predictor of myocardial infarction following surgery. Furthermore, according to the labeling for EPO targeting higher hemoglobin (13 to 14g/dL) compared to a lower range (9 to 11.3g/dL) increased the risk of death, myocardial infarction, stroke, and thrombotic events in patients *with CKD*.[29-30]

Screening for Potential Participants: A HIPAA waiver was obtained to allow the research team to screen the medical records of patients scheduled for CABG, valve or CABG/valve surgery at UTSW University Hospital eligible for participation in this study. At the initial consultation with the cardiothoracic service or through Patient Blood Management Clinic, patients who fulfill the initial entry criteria for the study will be invited to participate in this propensity-matched study for patients with "low preoperative blood counts (or anemia)". Patients who agree to be part of the study will be approached by members of the research team, who will explain the protocol in detail and will ask the patient to sign a written informed consent. Patients that become aware of the trial via the UT Southwestern clinical research website, will be referred directly to the clinical research nurse to answer all their questions and be encouraged to discuss possible participation with their surgeon during their next appointment.

Baseline Research Visit (7-28 days before day of surgery):

- Patients will be asked to sign the informed consent and HIPAA forms should they decide to proceed with the study.
- Patients will be escorted from the cardiothoracic surgery clinic by a member of the clinical research team or asked to come to the UTSW Patient Blood Management Clinic, Zale Lipshy University Hospital at 6201 Harry Hines Blvd.
- Data on demographics, vital signs, medical history, current medications, height, and weight will be recorded.
- We will review all available lab results.
- The patient will be enrolled into the treatment group.
- Treatment group patients will receive a single subcutaneous injection of EPO 300U/kg and an IV iron infusion of 510mg. Vital signs including heart rate, blood pressure, oxygen saturation, and temperature will be recorded before, during, and after drug administration.
- Patient will be monitored for any serious reactions during drug administration and for at least 30 minutes following each infusion. Serious reactions include anaphylaxis, chest pain, dyspnea, seizures, severe headache, fever, nausea, vomiting, and diarrhea, an increase in blood pressure greater than 20mmHg above baseline systolic, systolic BP greater than 180mmHg and/or diastolic BP greater than 100mmHg, hypotension.
- The visit will last approximately 1.5 hours.

Pre-op Visit (1-7 days before surgery)

- Patients in the treatment group will be seen again in a Patient Blood Management infusion room to receive a single subcutaneous injection of EPO 300U/kg and a 2nd IV iron infusion of 510mg, if iron reserves are believed to be inadequate (for a major hemorrhage) based on the result from the baseline iron panel and per Surveillance Strategy guidelines.

- Vitals signs, including heart rate, blood pressure, oxygen saturation, and temperature will be recorded before, during, and after drug administration.
- Patient will be monitored for any serious reactions (anaphylaxis, chest pain, dyspnea, seizures, severe headache, fever, nausea, vomiting, and diarrhea, an increase in blood pressure greater than 20mmHg above baseline systolic, systolic BP greater than 180mmHg and/or diastolic BP greater than 100mmHg, hypotension).
- Approximately 8mLs of blood will be drawn to obtain troponinT/CK-MB and reticulocyte count.
- The visit will last approximately 1 hour.

Day of Surgery

- We will monitor the patient's vitals (blood pressure, EKG, etc) as part of standard care.
- Approximately 8mLs of blood will be drawn to obtain hemoglobin concentration and reticulocyte count.

Post-Operative Dose

- Approximately 3mLs of blood will be drawn for a rotational thromboelastogram (RoTEM) measurement prior to redosing.
- Patients in the treatment group will receive a single subcutaneous injection of EPO 300U/kg two to four days following surgery, if they meet criteria as described in the surveillance plan.
- Vitals signs, including heart rate, blood pressure, oxygen saturation, and temperature will be recorded before and after injection.
- Patient will be monitored for any serious reactions (chest pain, dyspnea, seizures, severe headache, fever, nausea, vomiting, and diarrhea, an increase in blood pressure greater than 20mmHg above baseline systolic, systolic BP greater than 180mmHg and/or diastolic BP greater than 100mmHg).

Post-Operative Days #5, #7, #14

- On Day #5 approximately 8mLs of blood will be drawn to obtain a reticulocyte count, iron panel, AST/ALT.
- On Day #7 approximately 8mLs of blood will be drawn to obtain a reticulocyte count, CBC and creatinine (unless done as SOC).
- On Day #14 or at discharge approximately 6mLs of blood will be drawn to obtain a CBC and creatinine (unless done as SOC).

Clinical Outcomes

The primary objective is to assess the enrollment rate and adherence to the dosing protocol and

surveillance strategies. We define successful adherence as adhering to dosing in ≥90% of patients for ≥90% of the doses deemed appropriate by the surveillance strategy. Secondary outcomes will include:

1) changes in hemoglobin levels and reticulocyte counts within the two groups from baseline to the day of surgery (preop to POD#0) and POD#5;
2) proportion of patients receiving erythrocyte transfusions and number of blood products (RBC, platelets and plasma) utilized;
3) incidence of pre-defined clinical events (mortality, major cardiac, renal, neurological events [associated with anemia] and infection) in each of the study groups.

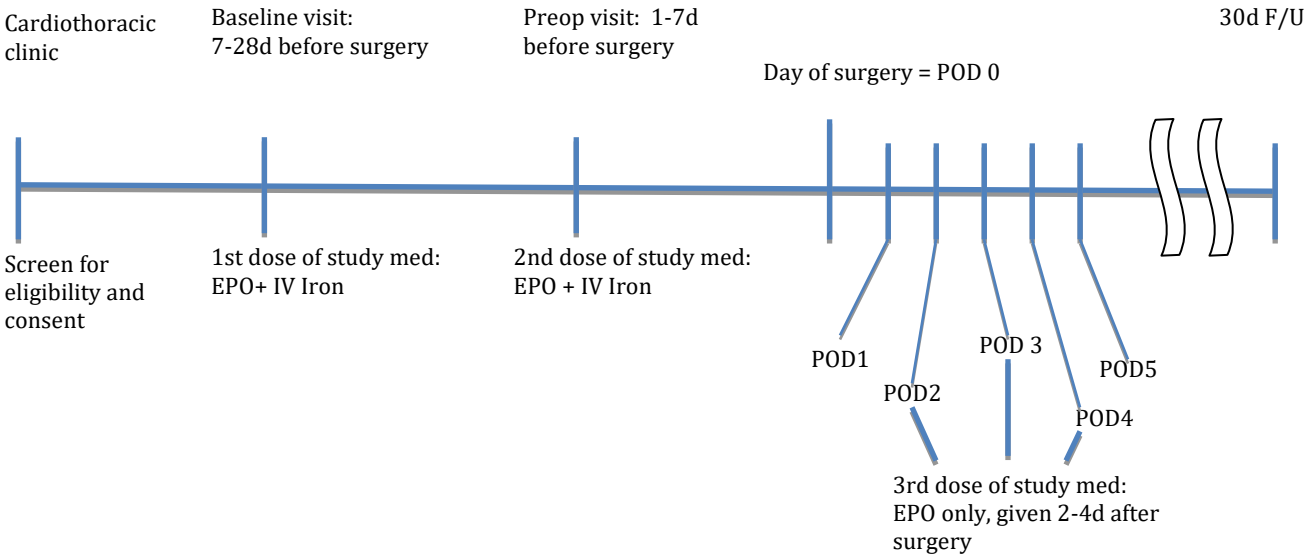
These events will include myocardial infarction, prolonged low-output state, stroke, encephalopathy, duration of mechanical ventilation, renal insufficiency, and mortality and dialysis dependence at 30 days or discharge. Data from this feasibility study will be used for the power analysis and design of the larger RCT.

Clinical events will be defined using the following criteria: Society of Thoracic Surgery (STS)[42] for stroke/transient ischemic attack (TIA), coma/encephalopathy, myocardial infarction (MI), prolonged ventilation, reoperation for bleeding or graft occlusion/revision, postoperative venous thrombosis, thromboembolic event, deep venous thrombosis and pulmonary embolism; RIFLE[43-44] for acute renal injury (AKI), National Healthcare Safety Network (NHSN)[45] for surgical site infections (SSI); Surgenor SD et al.[46] for low output heart failure (LOHF); any life-threatening events (i.e., subject was at substantial risk of dying at the time of the adverse event) and in-hospital or 30-day mortality based on observation. Outcome data will be collected via contact with primary physician, public record review or by a follow-up telephone call by the research nurse.

The cost of erythrocyte transfusions, EPO plus iron, direct hospital costs and direct margins associated with the care of those randomized in this pilot study will be recorded for future analysis of resource utilization. The duration of operating room time, intensive care unit and hospital length of stay will be collected. The total cost of erythrocyte transfusion will be based on four times the acquisition cost ($1,200.00)[47] The cost of EPO and IV iron will be calculated based on recommended manufacturer suggested retail price at the time of publication and will include activity based costs of administering these treatments based on the protocol outlined in this study.

IV. STUDY PROCEDURES:

Time Line of Pilot Study



Note: Supplementation with intravenous iron (feraheme; 510mg delivered as an IV infusion) will only be administered following the first two preoperative doses of EPO (shown in diagram).

Consort Diagram of Pilot Study:

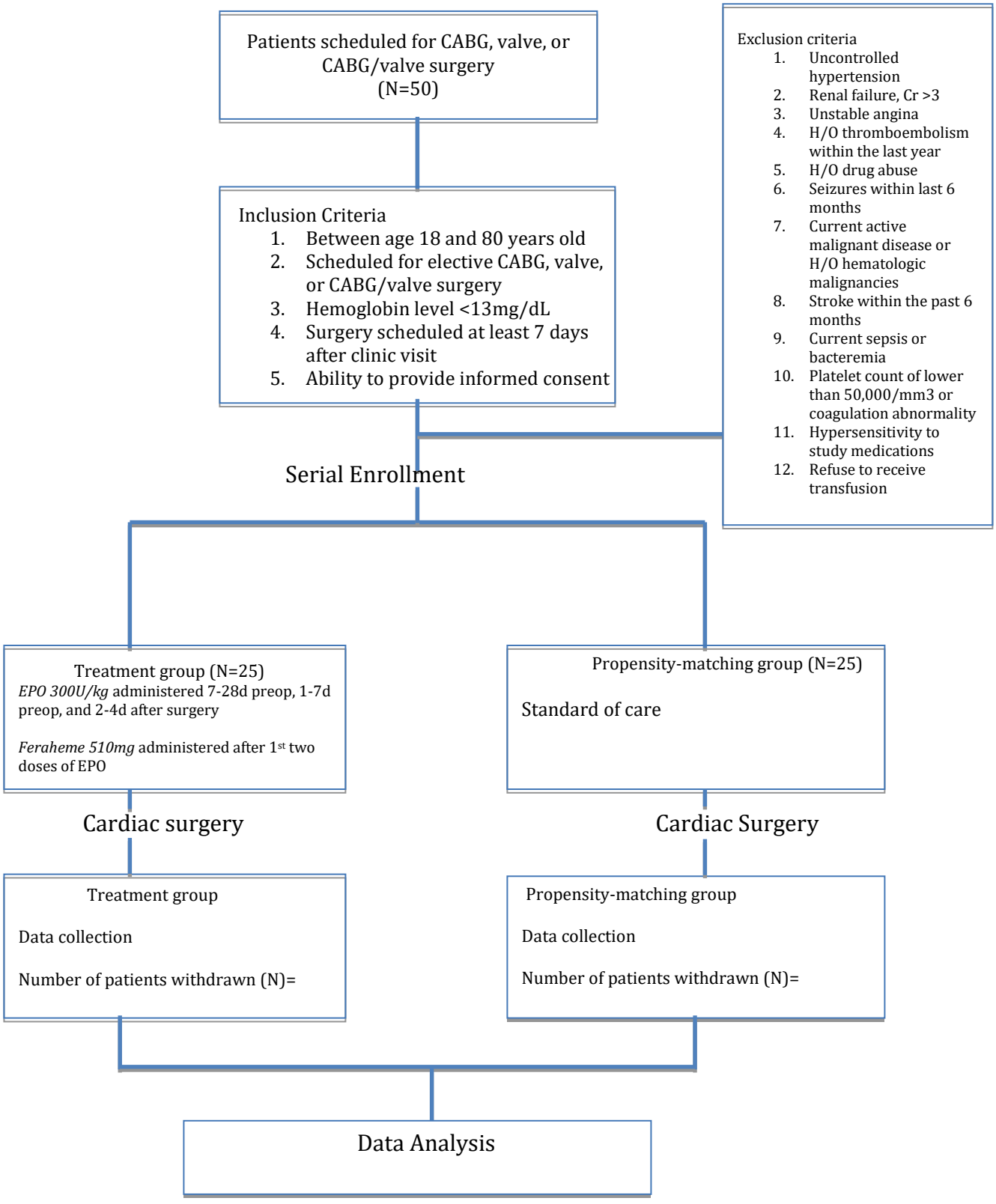


Table 1. SUBJECT SCHEDULE OF EVENTS

Test/evaluation & collected/required forms	7-28d PreOp	1-7d PreOp	POD0 PreOp	POD0 PostOp	POD 1	POD 2	POD 5	POD 7	POD 14
Inclusion & exclusion criteria	X								
Informed consent/HIPAA	X								
Demographics	X								
Medical History/Meds	X								
Physical examination	X	X	X	X	X	X	X	X	X
Body mass index	X								
Vital signs	X	X	X	X	X	X	X	X	X
ASA	X								
Laboratory									
CBC	S	S	S	S	S	S	S	S	S/X
Reticulocyte Count	S	X		X	S		X	X	
Iron panel**	S		X		S		X		
Creatinine	S	S	S	S	S	S	S	S	S/X
Troponin T/CK-MB		X		S	S	S/X			
AST/ALT		S			S		X		
Rotational Thromboelastogram (Rotem)+				S		X			
12-lead EKG	S	S	S	S	S	S	S	S	
Record of Erythrocyte transfusion	X	X	X	X	X	X	X	X	X
Estimated blood loss				X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X
Patient Survey	X								
Protocol Compliance	X	X	X	X	X	X	X	X	X

S = Standard of Care laboratory tests routinely ordered per ICU care team
X = Not routinely ordered laboratory tests; obtained for research purpose only.
*Will obtain hemoglobin and creatinine on POD14 or before hospital discharge (whichever event occurs first)
**Iron panel includes ferritin, TIBC, iron, transferrin
+ Will obtain RoTEM EXTEM 2-4 days after surgery

Adverse events and survival will be reviewed at the time of hospital discharge and 30d following surgery.

V. SUBSTUDY PROCEDURES

Our study does not include any sub-studies.

VI. CRITERIA FOR INCLUSION OF SUBJECTS:

The inclusion criteria of subjects are as follows:

1. The subject must be between the age of 18 and 80 years old.
2. The subject must be diagnosed with preoperative anemia, defined as hemoglobin <13.0g/dL.
3. The subject must be scheduled for elective cardiac surgery (CABG, valve, or CABG/valve), including both first time and repeat procedures.
4. Female subjects of child bearing potential must have a documented negative pregnancy test within 7 days prior to the procedure.

5. The subject must sign a written informed consent prior to the procedure, using a form that is approved by the UT Southwestern Institutional Review Board.
6. The subject must agree to be compliant and return for all follow-up visits.

VII. CRITERIA FOR EXCLUSION OF SUBJECTS:

The subjects will be excluded if they meet any one of the following criteria:

1. Uncontrolled hypertension (defined as systolic pressure greater than 180mmHg, diastolic pressure greater than 100mmHg, not adequately controlled by anti-hypertensive therapy at the time of procedure).
2. Current renal failure on dialysis or serum creatinine [Cr]>3.0mg/dL. [1]
3. Unstable angina (defined by chest pain and ECG changes indicating ischemia at rest).
4. Thromboembolism within the past year.
5. Current active primary or metastatic malignancy or history of myeloid malignancy.
6. Seizures within the past year.
7. History of stroke within the last 6 months.
8. Patients who have platelet count lower than 50,000/mm^3 or coagulation abnormality.
9. Sepsis or bacteremia defined by positive blood culture.
10. Patients who have known hypersensitivity to EPO or any of its components.
11. Patients who have known hypersensitivity to Feraheme or any of its components.
12. Patients who refuse blood transfusion, (i.e. Jehovah's Witnesses).
13. Pregnant or breast feeding.
14. Patients who are unable to provide informed consent or who has inability to understand or corporate with study procedure.

VIII. SOURCES OF RESEARCH MATERIAL

Data will be obtained from the patient's medical records EPIC and the Society of Thoracic Surgery (STS) database entries. Laboratory tests for reticulocyte count and additional serum ferritin, cardiac biomarkers, serum creatinine, thromboelastographic and liver transaminase measurements will be obtained specifically for research purposes. Other tests conducted (e.g. hemoglobin concentration, creatinine, EKG) will be part of standard of care (see Table 1 for details regarding standard of care and for research only).

IX. RECRUITMENT METHODS AND CONSENTING PROCESS

Potential subjects will be patients of the cardiothoracic surgeons. Patients fulfilling the entry criteria will be evaluated by their surgeon and invited to participate if none of the exclusion criteria are present and they are judged to be appropriate for the trial. Each patient will be asked if they are willing to speak with the research nurse and learn more about the study. If interested, the surgeon or their nurse, will notify the

clinical research nurse to discuss the details of the study either on the same day, by phone at another time, or by scheduling another appointment at their earliest convenience. Patients will be given an information pamphlet about the study.

The research nurse will provide a full description of the study to the patient and answer any questions that the patient might have. In order to minimize potential for undue influence or coercion, a section explaining the voluntary nature of the study will be included in the informed consent. The research nurse will also inform the patients that taking part in the study is entirely voluntary. The patient may decide not to endure the study and they may leave this study at any time. Choosing not to participate or leaving the study will not result in any punishment or loss of benefits to which they are entitled. The patient's decision will not affect his or her routine medical treatment and the relationship with those treating the patients or the study staff. Once patients have gained a full understanding of their rights and responsibilities and all pertinent aspects of the study, those who wish to participate in the study will be asked to sign an informed consent and a form for Authorization for Use and Disclosure of Health Information for Research Purposes (HIPAA). The patient's protected health information created or received for the purpose of this study is protected under HIPAA. Patient information will remain confidential unless the patient gives his or her permission to share it with others, or if the researchers are required by law to release it. Specific measures to protect the confidentiality and privacy of the patient are detailed in Section 11, "Procedures to Maintain Confidentiality" in the protocol. We do not request a waiver of informed consent, and we will not recruit vulnerable population in the study.

A copy of the consent form will be given to the patient for their review. Consented patients will be given the option of receiving their initial dose of study medication during the same visit, if appropriate, or scheduled at another appointment (7-28 days before their date of surgery) that either coincides with other hospital appointments or necessitates a separate research visit.

X. POTENTIAL RISKS

Risks associated with collection of blood for laboratory tests:

The total amount of blood collected for this study (if the blood tests have not been done as part of the routine care), will not exceed 8mLs per day. The blood sample will be drawn from a venous or arterial catheter, which will be placed in the operating room for routine care. If the IV access from which blood samples can be drawn has already been removed, blood will be drawn from an arm vein.

Risks associated with administration of medications:

Erythropoeitin: The safety of using EPO in an acute, perioperative setting has been well established in several meta-analyses.[1,4-5] The dosing schedule in this study is consistent with phase I and phase II human clinical trials[19-20] as well as multicenter clinical trials assessing the optimal and effective dosing of

EPO. The package insert for EPO does not recommend its use in patients undergoing cardiovascular surgery given the lack of sufficient safety and efficacy data; hence its use in this study would be considered “off-label”. As with all erythropoietic therapies, EPO may increase the risk of cardiovascular events, including death. In clinical trials, the most common adverse reactions, encountered in over 5% of EPO-treated perioperative patients, include nausea, vomiting, pruritis, headache, injection site pain, chills, deep vein thrombosis (DVT), cough, and hypertension. Due to the increased thrombotic risk in the perioperative period, DVT prophylaxis is recommended in all surgical patients receiving EPO.[29-30] Thrombo-prophylaxis in the cardiac surgery consists of sequential compression device, anticoagulation following valve surgery and aspirin following CABG surgery.

Because clinical trials have been conducted under widely varying conditions, adverse reaction rates observed in clinical trials of EPO may not reflect rates observed in our study. The black-box warning issued by the FDA for *chronic* use of erythrocyte stimulating agents in patients with end stage renal disease (ESRD) *and* cardiovascular disease (for increased risk of thrombotic and cardiovascular events) has been challenged by more recent publications outlining differences in the safety profile for short-term use in the perioperative setting. It is important to understand the differences in our patient population when comparing the adverse events listed on the package insert for this drug. First, the majority of adverse events reported by EPO clinical trials have been in chronic renal failure patients and in cancer patients receiving chemotherapy, whom we exclude from our study. Second, our protocol is a short-term (1-4 weeks) in patients experiencing moderate-to-high levels of acute hemorrhage (750mLs-1,500mLs). Third, all of the patients in our study will be anemic; thus the likelihood of having a hematocrit at a level likely to result in a thrombotic complications following CABG surgery is unlikely. Erythrocyte stimulating agents have been used in clinical practice at our institution for over 2 years and increases in the rates of seizure, thrombotic events, pure red blood cell dysplasia, or serious allergic reactions have *not* been observed in patients receiving these medications. The only side effect that has been observed is hypertension. In our study, treatment will be held in patients with blood pressure above 180/100mmHg.

Only one study in the cardiac surgery population has reported an uneven distribution of adverse events and mortality in the EPO-treated versus placebo group (6% vs. 0%, respectively)[15] Although the author of the study concluded there were no differences in adverse events between EPO and placebo-treated patients, an uneven distribution of mortality between the groups cannot be ruled out to any degree of certainty. Remarkably, given the small cohort size of this study, the probability is only 0.229 that, indeed, a statistically significant difference ($p<0.05$) exists between the EPO versus placebo treated groups.[48] Of note, an aggressive perioperative dosing regimen was utilized in the protocol of this study and the majority of these patients did *not* have preoperative anemia. In contrast, the remaining clinical trials, conducted over the past decade, have enrolled *anemic* patients and have failed to demonstrate a negative safety signal. More specifically, these trials found no observed difference in mortality, thrombotic

events, or serious adverse events associated with perioperative EPO use.[16-18]

This study protocol builds upon the safety profile established with using an *ultra*-short (<5 days) duration regimen recommended in the current practice guideline for cardiac surgery.[17-18,23,29,30] This study extends the dosing interval to 1-4 weeks in anemic patients using a well-established dosing regimen (300U/kg per dose).[29-30] Our risk:benefit assessment took into consideration that almost 80% of our patients with preoperative anemia have received erythrocyte transfusions in the past. The use of a novel surveillance strategy in our study provides additional safety measures to further minimize the risk of a thrombotic event.

Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD). It may cause serious hypersensitivity reactions, including anaphylaxis and/or anaphylactic reactions. In clinical cases,[46] serious hypersensitivity was reported in 0.2% (3/1,726) subjects. Other adverse reactions potentially associated with hypersensitivity (e.g. pruritus, rash, urticaria, or wheezing) were reported in 3.7% (63/1726) of these subjects. Hypotension may follow feraheme administration. In clinical studies, hypotension was reported in 1.9% (33/1726) subjects, including 3 patients with serious hypotensive reactions. Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis (a form of iron overload disorder). Administration of feraheme may transiently affect the diagnostic ability of MR imaging. Alteration of MR imaging studies may persist for up to 3 months following the last feraheme dose. In CKD patients, adverse reactions to feraheme reported in ≤1% of patients are nausea, dizziness, hypotension, peripheral edema, headache, edema, vomiting, abdominal pain, chest pain, cough, pruritus, pyrexia, back pain, muscle spasms, dyspnea, and rash.

There might be other side effects of the study medication that we cannot predict and possibly other side effects that are unknown at this time.

Risk associated with timing of surgery

The protocol is designed to result in no delay from the time when the patient is ready to schedule their surgical date to the day of surgery. The patient and treating physicians may elect to schedule surgery in a manner that would insure the full potential benefits of participation if deemed medically safe.

Risks involved with loss of confidentiality:

Any time information is collected there is a potential risk for loss of confidentiality. Every effort will be made to keep the patient's information confidential; however, this cannot be guaranteed.

XI. SUBJECT SAFETY AND DATA MONITORING

A. Adverse Events (AE):

Adverse events are events that involve physiological, social, or psychological harm to subjects or risks of harm to additional subjects or others. AEs include expected and unexpected harmful effects, and unexpected risks of an interaction or an intervention. AEs may be caused by: the test article or test procedure, other aspects of the interaction or intervention, the subject's underlying condition, or the subject's concurrent standard treatment. AEs may be definitely related, probably related, possibly related, unlikely to be related, or definitely not related *to the research*.

B. Method of Identifying, Recording, Monitoring and Reporting Adverse Events:

We will report all adverse events and other reportable incidences and occurrences to the IRB per reporting guidelines. Any adverse event will be documented of that event including a description, subject number, date, outcome, and follow-up.

C. Safety Endpoints:

The primary safety endpoints of the study are the incidence of adverse events associated with the use of the study medications. These include: hypersensitivity (e.g. pruritis, rash, and urticaria), hypertension, hypotension, bleeding, nausea, vomiting, injection site pain, deep venous thrombosis or other thrombotic complications. Surveillance for these adverse events will be conducted by direct observation (during drug administration), daily bedside visits by the research nurse for the first 7 postoperative days, review of the patient's medical record and listing any of these complication in the Society of Thoracic Surgery (STS) database. The definition of a stroke, myocardial infarction (MI), mesenteric artery occlusion or peripheral vascular event will be based on STS criteria.[37] Any event resulting in death from time of initial drug administration to hospital discharge will be recorded.

XII. PROCEDURES TO MAINTAIN CONFIDENTIALITY

We will collect data from lab tests and EPIC, the electronic medical record.

Raw data: We will remove personal identifying information of the patients from the raw data and replace them with coded IDs before data processing and analysis. Any materials containing personal identifying information will be stored in a locked cabinet in the principal investigator's office. After data entry, any materials containing personal identifying information will be promptly and securely returned to the principal investigator. Any materials with personal identifying information on them will be shredded before discard.

Computer files: Computer databases will contain only coded ID information. When computerized names and addresses are needed, they will be kept separate from other project data. All computer files will be password protected. We will destroy any computer disks with personal identifying information before discarding them. Personal identifying information will not be sent via e-mail.

Release of Data sets and Analysis of results: All data and information collected during this study will be considered confidential and remains the sole property of UTSW Medical Center. Data may be shared with AMAG Pharmaceuticals prior to any publications. All data used in the analysis and summary of this study will be anonymous, and without reference to specific subject names. Access to subject files will be limited to the Investigator, authorized clinical research staff and authorized Regulatory Authorities.

The principal investigator must authorize any release of information about the analysis results of the project. However, the UTSW institutional review board or government agencies such as the U.S Food and Drug administration (FDA) may look at and/or copy the patient's medical records for research, quality assurance, and data analysis.

XIII. POTENTIAL BENEFITS

Study participants could potentially increase their red blood cell mass and iron stores before going into surgery. Preoperative anemia is independently associated with a number of postoperative morbidities and mortality. Hence, the treatment has the potential to partially/completely correct preoperative anemia in patients undergoing cardiac surgery and lead to better postoperative outcomes. Anemia is also a major risk factor for allogeneic blood transfusion in the preoperative period. Transfusion has been demonstrated to be significantly associated with increased morbidity. These leading causes of transfusion-related morbidity and mortality are unrelated to viral transmission and include but not limited to changes in the immune system, which cause a stepwise increase in serious complications including postoperative infection, ventilator acquired pneumonia, central line sepsis, acute renal failure, cardiac events, and increased ICU and hospital length of stay. Thus, the treatment has the potential to reduce the transfusion requirement in these patients and improve postoperative outcome and decrease post-operative mortality. The study also has significant potential benefits to society. Transfusion is not only potentially hazardous for the individual patient, but it is also scarce and costly. Blood utilization in America is significantly higher than most Western countries and the gap is increasing. At this same time, the number of eligible donors has been declining because of a growing number of donor deferral criteria instituted to protect the blood supply. This supply and demand mismatch means that blood banks now have to work harder to recruit donors and blood shortages will become more frequent, leading to interruptions in hospital operations and the cancellation of elective surgeries. The total cost of transfusing patients exceeds blood acquisition cost by five times or greater when labor, supplies, blood administration and transfusion-related adverse event costs are considered. Hence, by potentially reducing the transfusion requirement in patients undergoing

cardiac surgery, the study has the potential to improve patient outcome, save lives, conserve a scarce resource, and also decrease the cost for hospitals.

XIII. BIOSTATISTICS

The analysis of this feasibility study will be mainly descriptive and will focus on confidence interval estimation. Results from hypothesis testing will be treated as preliminary and interpreted with caution, as no formal power calculations have been carried out.

Analyses will be performed using parametric and nonparametric univariate and multivariate (where appropriate) statistical methods. Univariate distribution of all variables will initially be performed assessing their distribution with the use of scatter plots and histograms. These results will be used as guidelines in the application of both univariate and multivariate techniques. For descriptive purposes, continuous variables with normal distribution will be described using means, variance and standard deviations; otherwise, medians, interquartile and full ranges will be used. For variables showing distributions that are significantly away from normality, nonparametric statistical tests will be applied. Differences will be considered significant when $P < .05$.

Dichotomous variables will be presented as percentages and analyzed using chi-square or Fisher's exact tests as appropriate. Student t tests or Mann-Whitney U tests will be used to assess differences between independent continuous variables. The analysis of paired continuous variables (such as changes of hemoglobin level or reticulocyte counts from baseline to the day of surgery) will be performed with paired student t tests or Wilcoxon signed rank tests for normally or non-normally distributed variables, respectively. Multivariable regression techniques, including linear mixed models, will be used to analyze differences in continuous variables measured at several different points during the study between the groups (such as hemoglobin level, reticulocyte count, creatinine, etc.) accounting for the within-subject correlation of the data. All statistical analyses will be performed with SAS® software (Version # 9.3, SAS Institute Inc. Cary, NC).

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Patient Questionnaire

You have agreed to participate in a research study testing whether it is practical to treat preoperative anemia up to 30 days prior to cardiac surgery. We think that treating anemia prior to cardiac surgery will result in better outcomes, but before we can conduct a study big enough to test that idea we first need to perform a smaller study to see whether our approach is feasible. We are interested in obtaining feedback about how important the treatment of preoperative anemia is to you. Answering the following questions will help physicians and hospitals understand your opinion of the approach being taken by this study.

A. Strongly Agree B. Agree C. Neutral D. Disagree E. Strongly disagree

1) I have concerns about receiving a blood transfusion.
   A B C D E

2) I would be willing to receive subcutaneous and intravenous injections preoperatively (to treat my anemia) if it could save me 1-2 units of red blood cell transfusions during or after my surgery.
   A B C D E

3) If it was considered to be medically safe by my cardiologist and surgeon, I would be willing to schedule my surgery up to 30 days after the decision to have surgery was made if this would decrease my chance of receiving a blood transfusion.
   A B C D E

4) I would be willing to make 1-2 additional trips to UT Southwestern in order to receive treatment for my anemia.
   A B C D E

5) The fact that UT Southwestern physicians are concerned about decreasing my chance of receiving blood transfusion(s) is important to me.
   A B C D E

6) Knowing a hospital is committed to treating my anemia preoperatively to avoid blood transfusion(s) could influence my selection where to have my surgery performed.
   A B C D E