VA Maryland Healthcare System

Cooperative Study

Transfusion Trigger after Operations in High Cardiac Risk Patients (TOP)

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PROTOCOL

Protocol
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CIRB APPROVED

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I. INTRODUCTION AND BACKGROUND

Blood is an indispensable product in modern medical practice.[1] Red blood cells (RBC) replace intravascular volume, improve oxygen delivery to tissues in situations of hemorrhage, and anemia[2] and consist one of the few treatments that adequately restore tissue oxygenation and maintain life when oxygen demand exceeds supply.[3,4] Since the decision of blood transfusion is primarily guided by the physiologic need to provide a critical mass of oxygen carriers to assure that metabolic processes proceed uninterrupted, a physiologic test would be ideal to assist with clinical decision-making. Unfortunately, such a test has not been discovered yet. The lack of sophisticated physiologically driven transfusion algorithms has led to the development of the "transfusion trigger" concept, which dictates that a specific level of hemoglobin (Hb) should be used to guide transfusion decisions. Historically, the widely accepted clinical standard has been to transfuse patients when the Hb level drops below 10gm/dl or the hematocrit falls below 30%. This "10/30 rule" was first proposed by Adams and Lundy in 1942 and served as RBC transfusion guide for decades[4,5], under the premise that a minimal RBC mass is critical to assure adequate oxygenation and avoid adverse cardiac events and death.

Blood is a finite resource whose collection depends on the availability of donors and its processing is costly and time consuming.[1,6,7,8,9,10-12] Therefore, clinicians sought to determine the safety of more restrictive blood transfusion strategies. In the first trial that challenged the 10/30 transfusion dogma, Hebert et al.[13] studied the impact of transfusion strategy in the ICU setting. The authors demonstrated that a restrictive transfusion strategy that accepted Hb as low as 7gm/dl did not have an adverse impact on survival when compared to a liberal strategy under which patients were transfused at trigger Hb < 10 gm/dl. Although a post-hoc analysis[14] of this trial that included a subset of patients with known ischemic heart disease demonstrated a trend for increased mortality in the restrictive transfusion group, this trial clearly indicated that restrictive transfusion could be safely practiced in some clinical settings.

Since then other randomized trials have examined the impact of transfusion strategy on specific patient populations using various combinations of restrictive and liberal thresholds. A trial in patients undergoing cardiac surgery[15] (transfusion thresholds at hematocrit < 24% vs. hematocrit < 30%) not only demonstrated that a restrictive strategy is safe, but also that the number of units of blood transfused was an independent predictor of mortality, as well as respiratory, cardiac, renal, and infectious complications. Obviously, generalizing these findings to other patient populations and surgical scenarios is not straightforward, as the patient population was either free of coronary artery disease, or had their diseased coronary arteries surgically bypassed during the index operation. In patients undergoing hip replacement,[16] transfusion trigger at Hb < 8 vs. Hb < 10 gm/dl did not adversely affect death or the ability to walk independently at 60 days after randomization. Results were similar in patients with septic shock[17] who were treated in ICU setting and were randomized to transfusion trigger of Hb < 7 vs. Hb < 9 gm/dl. At 90 days post-randomization the mortality was 43% vs. 45% for the restrictive and liberal group respectively (p=0.44), suggesting that a restrictive transfusion strategy is well tolerated in this patient population. Of note, only half of the patients in this trial underwent any type of surgery, and less than 15% had a history of underlying cardiovascular disease, a limitation acknowledged by the authors. Finally, the restrictive transfusion strategy was shown to be superior in patients with acute upper gastrointestinal bleeding who were assigned to thresholds of Hb < 7 vs. Hb < 9

gm/dl.[18] At six weeks, patients in the restrictive arm were more likely to be alive (95 vs. 91%, p = 0.02), and less likely to rebleed (10% vs. 16%, p=0.01) or have in-hospital complications (40% vs. 48%, p=0.02).

The findings of these trials, combined with the increasing RBC processing-related cost and the rising demand for blood services have created a major paradigm shift in transfusion strategies over the past several years. Published guidelines[2,19-21] and health policy statements[22] place a lot of emphasis on the need for restrictive transfusion thresholds in a variety of clinical settings; at the same time, the guidelines acknowledge[21] that a substantial area of uncertainty remains and concerns the patients with underlying cardiovascular disease, a population that is more likely than any other to be extremely sensitive to transfusion thresholds. Data on these high cardiac risk patients remain scarce, coming mainly from small trials and secondary analyses. Bush et al.[23] conducted a randomized trial of 99 patients undergoing major vascular reconstruction in order to evaluate a restrictive (trigger at Hb < 9gm/dl) vs. a liberal (trigger at Hb < 10gm/dl) transfusion strategy. These authors found equal morbidity and mortality (16% and 8% respectively) between the treatment groups. However, a subgroup analysis between an "anemic" group of patients who actually drop their postoperative Hb below 9 and the liberal group demonstrated trends for increased event rate in the restrictive arm (cardiac morbidity 23 vs. 14% and mortality 10 vs. 8% at 30 days for the anemic and liberal group respectively). In a separate study[24], 110 patients with acute coronary syndrome or stable angina who had Hb < 10 gm/dl were randomized to liberal (trigger at Hb < 10 gm/dl) or restrictive (trigger at Hb < 8 gm/dl or signs and symptoms of anemia) strategies. The primary endpoint (death, myocardial infarction or unscheduled revascularization within 30 days after randomization) occurred in 10.9% vs. 25.5% of patients in the liberal and restrictive group respectively (p = 0.076). More interestingly, mortality was substantially higher in the restrictive group (13% vs. 1.8%, p = 0.032). In the recently published TITRe2 trial, Murphy et al.[25] randomized 2007 patients undergoing cardiac surgery to a liberal (trigger Hb < 9 gm/dl) or a restrictive (trigger Hb < 7.5 mg/dl) transfusion arm. The primary endpoint (a composite of a serious infection or an ischemic event at 90 days after randomization) was not different between the two groups (35.1% vs. 33.0%, p=0.30). Analysis of the secondary outcomes, however, demonstrated that mortality at 90 days was more likely in the restrictive group (4.2% vs. 2.6%, p=0.045). The authors did not perform adjustment for multiple comparisons, and it still possible that the above finding is due to chance. However, a 69% relative risk difference in mortality favoring the liberal group is difficult to ignore, and underscores the urgent need for clarity on transfusion strategies in patients with underlying cardiovascular disease.

Taken together the above data in patients at high risk for adverse cardiac events raise serious concerns regarding the appropriateness of a restrictive transfusion strategy in this patient population. This uncertainty regarding transfusion thresholds is anything but trivial. In the United States one out of two males and one out of three females older than 40 years of age will develop ischemic heart disease (IHD) during their lifetime.[26] Approximately every minute an American dies from a coronary event, making IHD the leading cause of mortality in this country.[26] Since the fundamental pathophysiologic mechanism underlying coronary events is an imbalance between oxygen supply and demand, optimizing the oxygen carrying capacity of the blood is critical for these patients. As the world is progressively moving towards more restrictive transfusion standards, the unanswered question of transfusion thresholds in high cardiac risk

patients has created a knowledge gap that requires urgent attention. Published guidelines have made clinicians hesitant to transfuse these patients under a liberal strategy in order to minimize risks associated with a treatment the patient may not really need; on the other hand, the studies summarized above provide preliminary evidence that extrapolating transfusion strategies from other patient populations to individuals at high risk for coronary events is actually causing harm. Given the magnitude of IHD as health care problem, this uncertainty creates a critical patient safety issue.

In order to address this knowledge gap, we propose a randomized trial to compare two transfusion strategies in high cardiac risk patients undergoing vascular and general surgery operations. The study cohort will include patients with known history of IHD, or patients with history of peripheral arterial disease (PAD). PAD is a well-known marker of IHD and myocardial infarction represents the leading cause of mortality after PAD-related operations.[27] Furthermore, and unlike the patients undergoing cardiac surgery operations who have been included in published trials, patients in the proposed study will not have their coronary artery lesions routinely repaired during or prior to the index operation, and therefore their risk of cardiac events postoperatively will remain at least as high as it was preoperatively.

II. PRELIMINARY RESEARCH

a) The study proponent has performed a propensity score matched analysis of participants undergoing elective open surgical intervention for PAD.[28] The primary objective of this study was to assess the independent effects of nadir postoperative Hb (nHb) level and transfusion on a composite outcome of death or acute coronary syndrome (ACS) up to 30 days postoperatively. Secondary endpoints included perioperative wound and respiratory complications; and death or adverse cardiac events during an average follow-up of 24 months. A total of 1074 PAD-related operations were examined. In light of reports indicating a harmful effect of blood transfusion on mortality and cardiac outcomes, the analysis was adjusted for units of PRBCs transfused prior to the occurrence of any of the events that consisted of components of the composite outcome. Level of statistical significance in this study was set at alpha 0.0125 to account for the four comparisons performed when assessing the primary endpoint (two exposures tested against two individual outcomes).

TABLE 1: Effect of Nadir Hb and Units of Blood Transfused on a Composite Endpoint of Death, or ACS

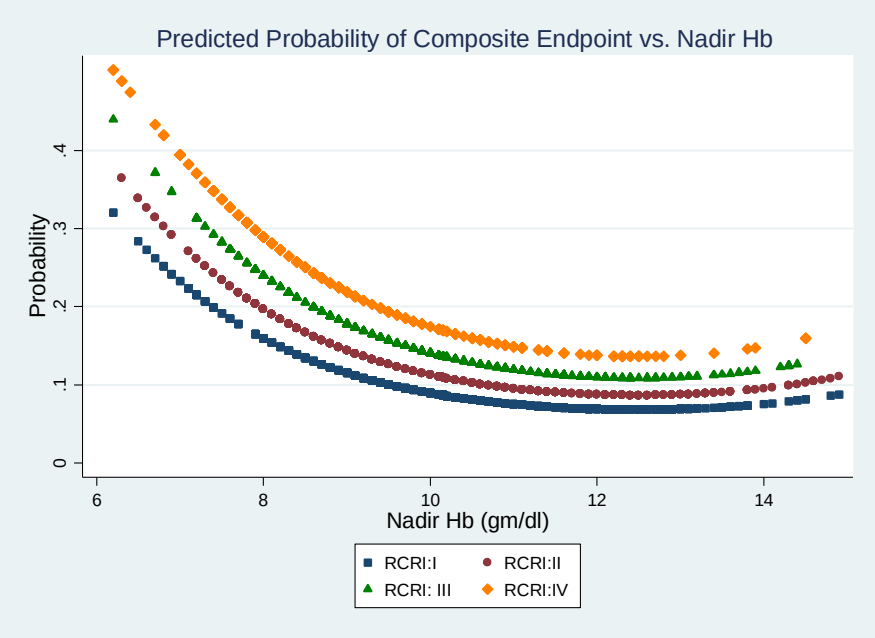
Variable	Odds Ratio	Standard Error	P-Value	95% Confidence Interval
Nadir Hb < 10gm/dl	Reference	Reference	Reference	Reference
Nadir Hb ≥ 10gm/dl	0.62	0.17	0.120	0.33-1.14
Transfusion units	1.11	0.05	0.025	1.01-1.22

Univariate analysis in this study demonstrated a relative protective but not statistically significant effect of nHb ≥10gm/dl on the composite endpoint of death or ACS (OR: 0.68, 95% CI: 0.54 to 1.19, p=0.12). On the multivariable model that included as predictors both nHb and units of blood transfused, nHb≥10gm/dl was again seen to have a relative protective effect on the composite endpoint, although again this difference did not reach statistical significance. (OR:

0.62, 95% CI: 0.33 to 1.14, p=0.12, Table 1). An intriguing observation of this study was that the event rate for the composite endpoint of death or ACS at 30 days was nearly 50% higher in the restrictive transfusion group (6.0% vs. 9.3%, Pearson's chi square test 0.052 on univariate analysis). After appropriate risk adjustment using propensity score matching this difference turned out to not be of statistical significance; however, the possibility remained that, in this patient population, a conservative transfusion strategy had a harmful effect that this observational study was simply too underpowered to conclusively demonstrate.

b) To address this possible power issue, Kougias et al conducted a larger single institution study[29] with primary endpoint a composite of all-cause mortality, MI (defined according to the Third Universal Definition of MI), acute renal failure (defined as acute kidney injury stage 3 per RIFLE criteria), stroke, or coronary revascularization within 90 days after the index intervention. In this new analysis a total of 2509 PAD-related operations were included. The composite endpoint occurred in 28.7% of patients with nadir Hb between 6-9gm/dl and 12.1% of patients with nadir Hb >9 gm/dl (p<0.001). Increasing nadir postoperative Hb demonstrated a strong curvilinear relationship with the composite outcome (OR 0.72, 95% CI: 0.74 to 0.85). Patients at higher baseline cardiac risk (as captured by Revised Cardiac Risk Index -RCRI) were at higher risk for the composite outcome across all ranges of postoperative nadir Hb; RCRI class II (OR: 1.8, 95% CI: 1.29 to 2.40), class III (OR: 2.07, 95% CI: 1.45 to 2.94), and class IV (OR: 2.38, 95% CI: 1.58 to 3.49) were associated with progressively increasing odds of the CE compared to RCRI class I. (Figure 1).

FIGURE 1. **Probability of the Composite Endpoint at Various Levels of the Postoperative Nadir Hb – Single institution data**



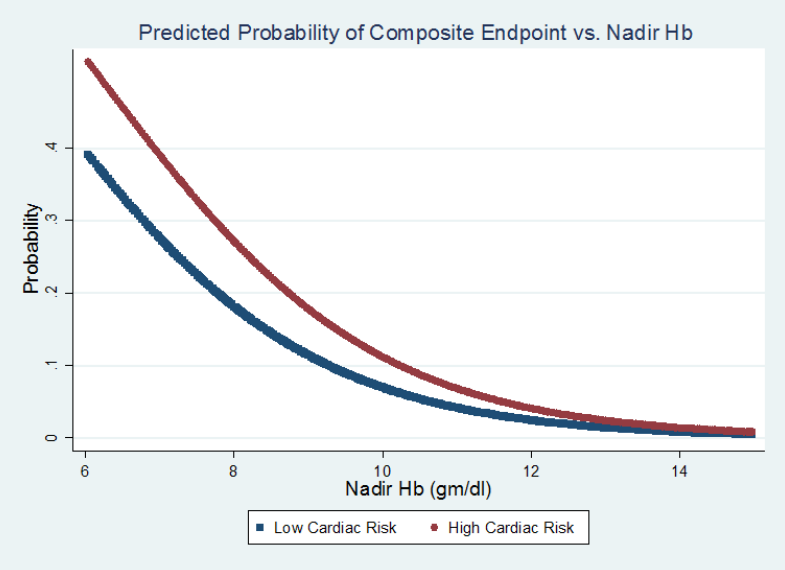
c) In light of these single institution results, the principal proponent and members of the planning committee conducted a large multicenter observational study with objective to assess the impact of postoperative anemia on patients at high risk for cardiac events who underwent major Vascular and General Surgery operations throughout the VA system between January 2000 and December 2014. Data from the Corporate Data Warehouse (CDW) database was used for this purpose. Patients who underwent operations for peripheral arterial disease (operative vascular bypass or major amputation) or elective (non-ruptured) aneurysm repair (either open or endovascular) were identified using Current Procedural Terminology (CPT) codes. Similarly, we identified patients who underwent the following General Surgery operations: open cholecystectomy or other complex biliary reconstruction, splenectomy, small bowel resection, colon resection, rectal resection, transabdominal esophagectomy, or open ventral hernia repair.

We collected data on preoperative and postoperative hemoglobin, creatinine, and troponin levels. The CDW database includes a time stamp that indicates the time of blood specimen was collected from the patient, along with the numerical result of the blood test. This greatly facilitated the precise assessment of the temporal relationship between time of operation, anemia, and creatinine or troponin elevation. In order to assess baseline comorbidities we accessed data on outpatient visits that had occurred prior to the time of the index operation. We assumed that a patient suffered from a particular comorbidity only when that comorbidity was entered as reason for the outpatient visit in at least two separate occasions that took place prior to the operative intervention. ICD-9 diagnostic codes were used for comorbidity identification.

The main outcome of this analysis was defined a-priori to be the same with the one of the proposed trial, and consisted of a composite of all-cause mortality, MI, acute renal failure, coronary revascularization (either percutaneous coronary intervention or open coronary artery bypass), or stroke, within 90 days from the index operation. Mortality was defined as death from any cause and was ascertained from the Vital Status patient file. MI was defined as a serum troponin I of at least 1ng/ml that was upwards trending in patients who either a) did not have elevated troponin preoperatively, or b) did not have any preoperative troponin I check. Clinicians do not routinely order postoperative troponin; thus, we assumed that that test was requested in patients with either EKG findings or symptomatology suggestive of MI, satisfying the Third Universal Definition. Although the 99th percentile upper reference limit of troponin I is 0.06 ng/ml or less for most assays used, we employed a more conservative cutoff of 1ng/ml to minimize overestimation of the endpoint by patients who might have had mild troponin elevation from non-ischemic causes. Acute renal failure was defined as acute kidney injury (AKI) stage 3 according to RIFLE criteria (serum creatinine at least > x3 of baseline, or serum creatinine > 4 mg/dl and rise > 0.5 from baseline). The creatinine value just prior to the date of the index operation was considered as baseline for those calculations. Urine output criteria are also included in the RIFLE classification; however, urine output cannot be reliably determined from a database review, and for this reason our assessment of AKI stage 3 from this analysis may have been conservative. Coronary revascularization was ascertained using appropriate CPT codes for either percutaneous or open coronary interventions. Finally, we attempted to identify postoperative stroke using the ICD-9 code 997.5; however, this return no events. Unlike the rest of the outcomes, extracting reliable stroke rates from the CDW database is not straightforward. Furthermore, single institution data have shown the 90 day stroke rate after vascular interventions to be low (approximately 1%), which is possibly why the database query returned

no events. We stratified the patients as being high risk for cardiac events if they had history of IHD, peripheral artery disease (PAD), or underwent a PAD-related operation. We ultimately collected information on 171,357 patients who underwent the target operations and were included in our analysis.

FIGURE 2. Probability of the Composite Endpoint at Various Levels of the Postoperative Nadir Hb – Multicenter data



Similarly to the single institutional analysis, a strong association was seen between increasing values of nadir postoperative Hb and freedom from the composite endpoint (OR: 0.566, 95% CI: 0.561 to 0.57, Figure 2). From the initial patient pool, 38,153 patients were at high risk for cardiac events and dropped their nadir postoperative Hemoglobin in the early postoperative period below 10 gm/dl, conditions that would make them eligible for the proposed trial. In this high cardiac risk patient population, the composite outcome occurred in almost 30% of patients with nadir Hb between 6-9 gm/dl (a subset that will represent the restrictive transfusion arm in the proposed study) and in 15% of patients with nadir Hb between 9-10 gm/dl (a subset that will represent the liberal transfusion arm in the proposed trial). Event rates for the composite and individual endpoints are summarized in TABLE 2 below:

TABLE 2. Composite Event Rates and Individual Event Rates among Veterans at High Cardiac Risks after a Surgical Procedure

Nadir Hb	Composite Endpoint	Death	MI	ARF	Coronary Revascularization
6-9 gm/dl	29.5%	15.3%	11.0 %	11.1%	0.4%
9-10 gm/dl	15.0%	6.9%	6.2%	4.1%	0.3%

III. SIGNIFICANCE AND RELEVANCE TO VETERANS

The proposed trial is uniquely positioned to address the knowledge gap of appropriate postoperative transfusion thresholds in high cardiac risk patients. Given the high prevalence of IHD and the potentially devastating clinical consequences of inappropriate transfusion strategy selection, identifying the optimal transfusion strategy for this patient population is critical for patient safety. If the proposed trial demonstrates that the liberal strategy is superior, then outcomes in patients at high cardiac risk will improve, as clear guidance will be provided to clinicians that restrictive policies are not appropriate for this patient population. Conversely, if the restrictive strategy proves to be safe in these patients who represent a subset that is the least likely to benefit from such a strategy, then a well-informed and generalizable statement supporting restrictive blood transfusion strategy in practically every patient population can be made. This will result in policy changes that will reduce unnecessary transfusions, and transfusion-related complications and cost. Therefore, the proposed trial is well positioned to have substantial clinical and policy implications nationally and internationally regardless of its outcome.

Optimizing transfusion thresholds in high cardiac risk patients is highly relevant to the VA and its mission. Veteran patients are older and have higher incidence of cardiovascular disease than the general US population.[30] Furthermore, the cardiovascular risk profile of Veterans has been shown to deteriorate over time, with increasing rates of diabetes, obesity, and left main coronary artery disease.[31] As a result, IHD is highly prevalent in the VA system, where it represents the leading cause of mortality and third leading cause of hospitalization.[32,33] For these reasons, optimizing transfusion thresholds in high cardiac risk patients will have a particular impact among Veteran patients.

IV. STUDY OBJECTIVES

The goal of the proposed study is to determine whether a liberal transfusion strategy (transfusion trigger at Hb < 10 gm/dl) in Veterans at high cardiac risk who undergo major open vascular and general surgery operations is associated with decreased risk of adverse postoperative outcomes compared to a restrictive transfusion strategy (transfusion trigger at Hb < 7 gm/dl).

A. Primary Objective

Objective 1: To examine the effect of transfusion strategies on a composite endpoint of all-cause post-randomization mortality, myocardial infarction (MI), coronary revascularization, acute renal failure, or post-randomization stroke in Veterans at high cardiac risk undergoing open surgical interventions

Hypothesis 1: A significantly smaller proportion of participants receiving blood under a liberal transfusion strategy will experience the composite compared to participants under restrictive transfusion strategy at 90 days after randomization.

B. Secondary Objectives

Objective 1: To examine the effect of transfusion strategies on post-randomization infectious complications.

Hypothesis 1: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience post-randomization infectious complications compared to participants under restrictive transfusion strategy at 90 days after randomization.

Objective 2: To examine the effect of transfusion strategies on post-randomization cardiac complications other than MI.

Hypothesis 2: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience post-randomization cardiac complications other than MI compared to participants under restrictive transfusion strategy at 90 days after randomization.

Objective 3: To examine the effect of transfusion strategies on all-cause mortality during the one year post-randomization follow-up.

Hypothesis 3: A smaller proportion of participants receiving blood under a liberal transfusion strategy will die from any cause compared to participants under restrictive transfusion strategy during one year follow-up after randomization.

Objective 4: **To examine the effect of transfusion strategies on a composite endpoint of all-cause post-randomization mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke at 30 days after randomization**.

Hypothesis 4: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience the composite endpoint compared to participants under restrictive transfusion strategy at 30 days after randomization.

Objective 5: To examine the effect of transfusion strategies on the length of hospital stay

Hypothesis 5: Liberal transfusion strategy will lead to a shorter length of hospital stay.

C. Tertiary Objective

Objective: To examine the effect of transfusion strategies on the components of the primary endpoint.

Hypotheses: A smaller proportion of participants receiving blood under a liberal transfusion strategy will experience post-randomization death from any cause, MI, coronary revascularization, acute renal failure, or post-randomization stroke, compared to participants under restrictive transfusion strategy at 90 days after randomization.

V. STUDY OUTCOME MEASURES

A. Primary Outcome

The primary outcome is defined as a composite endpoint of all-cause post-randomization mortality, myocardial infarction (MI), coronary revascularization, acute renal failure, or post-randomization ischemic stroke up to 90 days after randomization.

MI will be defined using the Third Universal Definition of Myocardial Infarction.[34] (Please see Appendix I.)

Acute renal failure will be defined as Acute Kidney Injury stage III according to RIFLE criteria: Serum creatinine rise greater than 3 times that of baseline creatinine; or if baseline serum creatinine is greater than 4 mg/dl, then rise more than 0.5 mg/dl compared to baseline; or urine output less than 0.3ml/Kg/hr for 24 hours; or anuria for 12 hours. Baseline creatinine will be considered the creatinine upon admission prior to the index operation. The above urine output criteria will be only used for patients who are in the ICU and have precise monitoring of their urinary output. For patients on the surgical floor only serum creatinine changes will be used for assessment of this endpoint.

Coronary revascularization will be defined as a coronary artery bypass graft, or percutaneous coronary intervention (either angioplasty or stenting).

Stroke will be defined as new unilateral neurological deficit that lasts for more than 24 hours, and is confirmed by a brain imaging modality (either computed tomography or magnetic resonance imaging study) demonstrating new brain infarct.

B. Secondary Outcomes

Outcome 1: A composite endpoint of post-randomization infectious complications at 90 days post-randomization: Infectious complications will include wound infections, pneumonia, and sepsis.

Wound infection will be defined according to the Centers for Disease Control and Prevention (CDC) guidelines as a) positive wound culture, or b) drainage of pus from a wound, or c) suspicion of wound infection that was drained operatively.

Pneumonia will be defined according to the CDC definition as chest radiograph or imaging with new or progressive infiltrate, consolidation, cavitation, or pleural effusion and any of the following: new onset of purulent sputum or change in character of sputum, or organism isolated from blood culture, trans-tracheal aspirate, bronchial brushings, or biopsy.

Sepsis will be defined as a combination of two of the following systemic inflammatory response syndrome (SIRS) criteria, **plus** suspected or present source of infection. SIRS criteria will

include the following: temperature greater than 38C, heart rate greater than 90 beats/min, WBC > 12,000 or < 4,000, or > 10% bands.

Outcome 2: A composite endpoint of cardiac complications (other than MI) at 90 days post-randomization: Cardiac complications will include new cardiac arrhythmias that necessitate new treatment, new or worsening congestive heart failure (CHF), and cardiac arrest not leading to death.

The diagnosis of cardiac arrhythmias will be based on EKG findings. Only arrhythmias that result in initiation of new treatment regimen (to include medications, implantable devices, or surgical intervention) during hospitalization will be recorded.

CHF will require at least one of the following symptoms or signs new or worsening: dyspnea at rest, orthopnea, or paroxysmal nocturnal dyspnea **and** radiological evidence of heart failure or worsening heart failure **and** increase/initiation of established treatment.

Cardiac arrest will be defined as the cessation of cardiac pump function activity that results in loss of consciousness and absence of circulating blood flow as evidenced by absent carotid pulse. Only episodes of cardiac arrest that are reversed will be collected under this endpoint. If they are not reversed the event will be categorized as death.

Outcome 3: All-cause mortality at 1 year after randomization.
We will determine vital status by telephoning participants after hospital discharge, by searching the electronic medical record and the VHA Death Ascertainment File (DAF).

Outcome 4: A composite endpoint of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization ischemic stroke at 30 days after randomization.

Outcome 5: Length of hospital stay.

C. Tertiary Outcomes

We will examine individual rates of the outcomes that consist of individual components of the primary endpoint.

VI. SUMMARY OF STUDY DESIGN

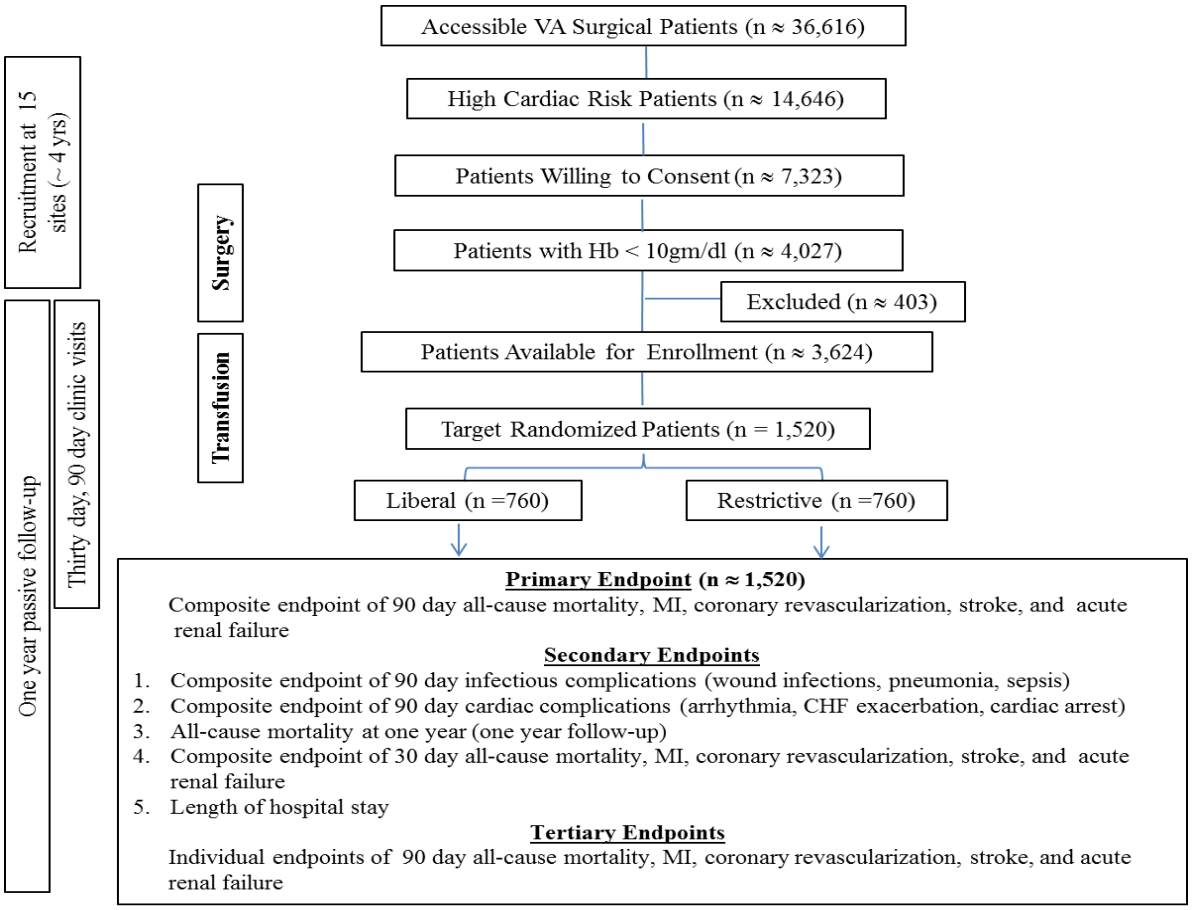
The study is a parallel, single-blind, controlled, superiority trial in which participants will be randomized to a restrictive or a liberal transfusion group. This study will randomize 1520 Veterans at 15 VA Medical Centers. The total recruitment period will be approximately 4 years which will be followed by a 3 month active and 9 month passive follow-up period. The duration of the study will be approximately 5 years. Consent for the study will be obtained prior to the index surgical intervention at the clinic visit or, in case of inpatients, at the hospital ward pre- or postoperatively. Randomization will be performed via a central telephone randomization system once the participant has a confirmed Hb < 10gm/dl. Active follow up will be up to three months

after randomization. Passive follow up will be from 3 months to one year after randomization. The study flow is shown in FIGURE 3. There will be no blinding at the treating physician level; however the participants and the Endpoint Committee will be unaware of group allocation.

Follow up forms will be filled out during two postoperative clinic visits that will be after the 30th and 90th post-randomization days. Participants who cannot make the clinic visits will be assessed by phone call follow-up, during which they will be asked specific questions to ascertain whether signs or symptoms related to any of the endpoints have developed. In addition, the electronic medical record, will be assessed to collect relevant information. If a participant gets re-admitted at any time after discharge and within 90 days after randomization, the electronic medical record will be examined for the presence of any of the diagnoses that consist part of either the primary or any other endpoints. If the participant has been admitted to a non-VA facility, a full copy of hospital records from that admission will be obtained and assessed for the presence of any of the outcomes. History and physical, consultation notes and progress notes will all be reviewed. Furthermore, particular attention will be paid to laboratory reports for troponin, creatinine, CK-MB (if available), and WBC levels, reports of cardiac echograms, radiology reports, and results of cultures (blood, wound, sputum). Participant agreement for release of information to the study personnel for all postoperative hospital visits that occur within 90 days after randomization will be obtained as part of the original consent form.

Assessment of one year mortality will be performed as part of a passive follow up performed by the Chairman's office via examination of the electronic medical record, follow up phone calls, and search of national databases documenting mortality.

FIGURE 3: Study Flow



VII. PARTICIPANT POPULATION

All Veterans who are scheduled to undergo vascular or general surgery at a VAMC will be invited to participate in this trial. The inclusion and exclusion criteria are outlined below.

A. Inclusion Criteria

1) Male and female Veterans older than 18 years of age who have postoperative Hb < 10gm/dl within 15 days after the index operation

2) Patients undergo an operation in either one of the three following categories
   a. Veterans who undergo PAD – related operations including but not limited to the following: aortobifemoral or aortobiiliac bypass, open abdominal aortic aneurysm repair with simultaneous repair of aortoiliac occlusive disease, visceral bypass, iliofemoral bypass, femoral bypass or endarterectomy, infrainguinal bypass; thromboembolectomy; supra-aortic trunk bypass or endarterectomy, carotid endarterectomy, and major lower extremity amputations (transfemoral, through the knee, or transtibial)

b. Veterans with past medical history of ischemic stroke/TIA of likely carotid origin, or history of IHD (defined as known prior MI, EKG findings consistent with prior MI, prior percutaneous coronary intervention, prior coronary artery bypass surgery, history of angina for which the patient is currently receiving treatment, or stress test indicating myocardial ischemia), or history of PAD (defined as prior intervention for PAD or ABIs < 0.9) who undergo the following General Surgery operations: Open cholecystectomy or other open complex biliary reconstruction (such as open common bile duct exploration for stones, reconstruction as part of oncologic operations such as palliative pancreatic cancer procedures), open or laparoscopic small bowel resection, pancreatectomy, colon resection, colostomies (reversals and takedowns), intestinal anastomosis takedown and revision, rectal resection, splenectomy, transhiatal esophagectomy, liver resection, gastric operations (resections or repairs), gastric bypasses, adrenalectomy, major diaphragmatic hiatal hernia repair, Nissen fundoplications, and ventral hernia repair
c. Veterans with past medical history of ischemic stroke/TIA of likely carotid origin, or history of IHD, or history of PAD (defined as prior intervention for PAD or ABIs < 0.9) who undergo the following Vascular Surgery operations: Open aneurysm repair (including but not limited to carotid, subclavian, abdominal aortic, iliac, femoral, or popliteal aneurysms); and complex endovascular aneurysm repair (defined as fenestrated endograft, or endograft with need for iliac conduit, or endovascular aneurysm repair with simultaneous femoral artery reconstruction or bypass). Subclavian/vertebral bypasses and transpositions are eligible with a history of PAD/IHD/ischemic stroke.

Patients undergoing the above procedures will be included in the study regardless of their preoperative Hb level, and regardless of preoperative or intraoperative transfusion they might have received. For non-compressible arteries and patients with diabetes, toe pressures (<60 mm Hg) may be used to identify prevalence of PAD.

B. Exclusion Criteria

1) Veteran unable to consent
2) Veteran unwilling to follow protocol (such as Jehovah's witnesses)
3) Veteran with known history of hereditary anemias such as Thalassemia or Sickle cell disease
4) Veteran with known history of hereditary bleeding disorders, such as factor VIII or factor IX deficiency
5) Veteran with prior history of adverse reaction to blood administration, such as fever, rash, or hemolysis
6) Veteran does not speak or understand English
7) Veteran hemodynamically unstable (systolic blood pressure <90 and heart rate >100 that persists for at least 30 minutes) or in cardiogenic shock for ≥ 48 hours after the index procedure

8) Veterans participating in another interventional trial
9) Pregnancy in female Veterans
10) Veteran is a prisoner or in custody of law enforcement
11) Prior randomization in the CSP#599
12) Patients who are known to have tested positive for COVID-19 and have not recovered prior to consent will not be consented. Any participant who is known to have a positive COVID-19 test during the screening process and has not recovered will be excluded prior to randomization.
Recovery from COVID-19 is defined as a patient who is asymptomatic (per local preoperative clearance policies) and at least 10 days post a positive test.
Note: Patients may be screened, consented, and randomized once recovered, if not previously randomized. Veterans who test positive *after randomization but before discharge* must be terminated for study ineligibility. Veterans who test positive *after randomization and after discharge from the index admission*, may continue to participate in the study as long as follow up is completed remotely.

C. Recruitment

The site coordinator along with the local site investigator (LSI) will be primarily responsible for identifying each potential participant scheduled for an open surgical procedure. At the beginning of the study, vascular and general surgeons performing the operations of interest at a VAMC will be personally contacted by the Site coordinator to discuss logistical and procedural issues related to recruitment. Surgeons (both vascular and general surgeons) have been contacted in 15 primary and 8 back up VAMCs and have confirmed interest in participation in the study.

The methods to identify and recruit Veterans with a proposed surgical procedure will be as follows; a) for outpatients seen in the clinic, any physician (resident or attending) can explain the study to the participant in collaboration with the LSIs, Site Coordinator, Research Assistant, and study team, check the participant's eligibility for the study and notify the site coordinator to obtain informed consent at the time consent is obtained for surgery. Participants will be given up to 2 days to decide whether or not they would like to participate in this study. Participants will receive a signed and dated copy of the informed consent (10-1086) and a signed and dated copy of the HIPAA authorization. To optimize recruitment, the site coordinator will maintain a list of outpatient preoperative clinics in which Veterans undergoing the operations of interest are seen, and will review with physicians who staff those clinics, the inclusion and exclusion criteria for the study. Furthermore, the site coordinator will be present during clinic hours in order to provide immediate feedback and answer questions with respect to study eligibility; b) for inpatients, any physician can explain the study in collaboration with the LSIs, Site Coordinator, Research Assistant, and study team, check the participant's eligibility for the study and notify the site coordinator to obtain consent. To assure that no participants are lost, the site coordinator will review the surgery schedule two days ahead of time to assure that all eligible inpatients scheduled for an open operation have been approached and the study has been discussed with them. If unable to obtain consent preoperatively for any reason, participants can be approached postoperatively, provided they are able to provide informed consent. Post-operative consent must

be completed within 48 hours of the procedure; if the procedure was completed on a Friday, consent may be obtained the following Monday for a 72-hr. consent window.

To assess feasibility of this study within the VHA system, we estimated volume for the operations of interest by a) querying the Corporate Data Warehouse (CDW) VA database using ICD-9 and CPT codes, and b) conducting a survey of possible Site Investigators in individual participating VAMCs who have confirmed interest in participating in the trial.

a) According to the VA CDW database that tracks operative interventions using ICD-9 and CPT codes, the average number of Veterans who had vascular and general surgeries from 2011-2014 were 9,154 per year among 15 VA medical centers who have agreed to participate in the proposed trial. For four-year recruitment time, we project that Veterans who will have the surgical interventions of interest will be over 36,616. We estimated that 14,646 of the Veterans who undergo the operations of interest have high cardiac risk (approximately 40%).This assumption is based on our review of the CDW database that included approximately 171,000 patients as described on page 5. Among these high cardiac risk Veterans, we assume that 7,323 (50%) will agree to be randomized to the study (agreement to randomization has been approximately 70% in other published trials on the topic; we prefer to err towards a more conservative side). Of these consented Veterans, 4,027 (55%) will drop their postoperative Hb level below the threshold of 10 gm/dl to be eligible for randomization (this assumption is again based on the CDW data analysis described on page 5). Among those who have Hb level below 10 gm/dl, 10% are assumed to fall under the exclusion criteria (approximately 403), which will yield over 3,624 eligible Veterans available for randomization; while the targeted sample size is 1,520 participants (Figure 3). Simply, according to the above estimations, approximately 10% (40% ×50%× 55%×90%) of the Veterans who undergo the operations of interest will be eventually randomized. Put it differently, in the sites that have already agreed to participate in the trial an average of 610 operations per facility per year can be expected. In the proposed scenario 10% of these Veterans will be ultimately randomized then we anticipate recruiting 61 Veterans per site per year (or 5 Veterans available per site per month).

b) In addition to the above analysis, we have conducted a survey of the possible Site Investigators in these 15 facilities that have expressed interest in participating in the trial, as well as in 8 additional facilities that will serve as back up sites. These Site Investigators are surgery section leaders and have been selected on the basis of clinical experience (80% of them have been in practice for more than 10 years), and also experience with prior CSP studies (65% of these Site Investigators have in the past participated in a CSP trial). According to the survey, vascular surgeons estimate that on average 3.5 vascular surgery patients per month per facility can be recruited, whereas general surgeons estimate that on average 3 general surgery patients per month will be recruited. This represents a minimum of 6 patients per month available for recruitment, an estimate fairly close to the results of the CDW database analysis.

Despite those estimates, we take a more conservative approach to assume that on average each participating site will recruit approximately 3 patients per month. Target sample size is 1,520 Veterans. The enrollment period will be approximately four years based on 15 sites and 3

participants/month/site rate of enrollment (starting with eight sites for the first year and adding the remaining seven sites on the second year). In total, 4,560 participants will be consented; we estimate that 1,520 participants will be eventually randomized. In each site, the number of participants enrolled annually will not exceed 250. We estimate that 102 participants per site will be randomized. It is possible that some sites with higher surgical volumes will randomize more than 102 participants. This is acceptable.

Depending on study progress and recruitment, if only one service (vascular or general) of a high surgical volume VA Medical Center is interested in participating, the site may be included in the trial.

c) During the first year, eight sites including three Network of Dedicated Enrollment sites (NODES) will be launched. This will enable the study Executive Committee to monitor the recruitment rates at these sites during the first year of the study's conduct. If the recruitment rates at these sites do not meet the expected rate (3 participants/site/month), measures will be taken by the study leadership to ensure meeting the recruitment target as follows: a) Targeted intervention and surgeon education will be performed if changes in a specific site's human resources are thought to be the reason for poor recruitment (e.g. if new surgeons have arrived and are not supportive of the study); b) Site's overall surgical volume will be reassessed and if a substantial decline is seen, one out of eight available back up sites will be chosen to replace underperforming sites; c) In the unlikely event that poor recruitment is an issue for multiple sites, the patient population will be expanded to include high cardiac risk patients who undergo major orthopedic operations, such as knee and hip replacement, and major open fracture repair.

VIII. HUMAN RIGHTS ISSUES AND INFORMED CONSENT

CSP follows the principles of medical research involving human participants as outlined in the Declaration of Helsinki.

Informed consent will be obtained from all CSP study participants prior to participation in this study. Informed consent requires that the participant understand and agree to the study procedures, treatments, and risks. The participant will be explained the voluntary nature of participation in the research study and can withdraw from participation without penalty at any time. It will be communicated that current treatment, future medical care, and benefits will not be dependent on participation in the research. The participant must have sufficient time to read and discuss the informed consent document prior to signing.

The process of informed consent must occur verbally with the study participant. In discussion of the consent form with the participant, the investigator (or other study personnel identified in this protocol to conduct the informed consent process) may provide additional details beyond those contained in the consent form. Additional information may not represent any significant additions, deletions, or modifications to the information in the informed consent document. The research participant will be provided with a paper signed and dated copy of the consent form and any supplementary materials to read and review prior to consent.

The informed consent document will contain all elements as outlined in VHA Handbook 1200.05 as required by the Common Rule, and will meet the requirements of 21 CFR 50.25. The consent will be documented on VA Form 10-1086 Research Consent Form. The VA CIRB or other IRB of record for the study will approve the consent form prior to its use.

An IRB approved most current version of the informed consent must be signed and dated by the study participant and the person obtaining the informed consent. The original signed and dated informed consent document will be placed in the investigator's research file. Copies of the signed and dated informed consent document will be provided to the participant at the time of consent and to the CSPCC per instructions in the Operations Manual.

The informed consent process will be documented in a detailed progress note prior to study participation.

A separate written HIPAA authorization for the use of individually identifiable health information must be signed by the research participant unless a waiver for HIPAA authorization has been granted by the VA Central IRB or IRB of record for the research.

Data will be retained after the end of the study as per VA and IRB regulations.

IX. EVALUATION PROCEDURES

A. Screening

The Site Study Coordinator will be primarily responsible for identifying each Veteran scheduled for an open surgery at the clinic. Each site will obtain a waiver of informed consent/HIPAA for pre-screening purposes from the VA Central IRB.

B. Randomization

After an eligible participant provides informed consent, the study staff will complete all sections of the pre-randomization forms except for the postoperative Hb measurements. The clinical site coordinator will be responsible for tracking the postoperative Hb levels and identifying participants whose Hb level is below 10 gm/dl and therefore eligible for randomization. iStat hemoglobin values may not be used as the basis for randomization/transfusion decisions. The CSPCC staff will prepare randomization schedules for each clinical site participating in the study. The study randomization to either liberal or restrictive transfusion policy will be done by an Interactive Touchtone Telephone Randomization System (ITTRS). A stratified block randomization scheme will be used to randomize participants in the two transfusion groups. The stratifying factors are clinical site and revised cardiac risk index (RCRI) class. Following participant randomization, clinical data and transfusion records will be obtained by the study team.

C. Participant Assessments

1. Baseline Assessment

Baseline assessments will be collected the time between identification of an eligible participant and either randomization or 15 days after surgery (or until discharge, whatever comes first) including revised cardiac risk index (RCRI), patient history, hemoglobin level, EKG diagnosis, troponin, serum creatinine, albumin, and patient clinical status. Data collected during this period is used primarily for monitoring recruitment and randomization status. We will maintain the information of all identified potential participants. This will be accomplished by completing the screening form for every participant presenting to the clinical site for eligible operations including those who are excluded from the study for any reason. Following is a list of assessments that we plan on collecting:

Screening Record: To compare patient screened (but not randomized) to patient randomized in this study, a comprehensive screening assessment will be completed for all potentially eligible subjects scheduled to receive an open surgery procedure at a participating center by the Study Coordinator.

Demographic: The clinical site coordinator will collect demographic and participant information. The demographic information will include participant's age, gender, race, marital status, etc.

Clinical Data: The site coordinator will also collect clinical data using information from the medical record and consult with the surgeon as needed. These will include height, weight, last preoperative serum Hb, albumin, blood pressure, and history of comorbidities, including coronary artery disease, end-stage renal disease, chronic obstructive pulmonary disease, hyperlipidemia, diabetes mellitus, and hypertension.

To assure that MI or acute renal failure have not occurred prior to the time of randomization the patient's chart will be reviewed for Troponin, EKG, and serum creatinine. If these values are available in the 24 hrs. prior to randomization, they will not be collected again. If unavailable within this period, EKG, serum creatinine, and troponin data will be collected within 24 hours from the time of randomization. If available at the institution, CK-MB will also be collected (not required).

We will also collect information on prior history of MI, coronary artery bypass, and stent placement. Furthermore, intraoperative assessments will be collected during the surgical procedure, such as type of operation, amount of intraoperative blood loss, intraoperative transfusion, amount and type of fluids administered, and length of the operation.

Lab, transfusion, EKG ordering procedures: Once the participant is randomized, a study team member should enter a CPRS note indicating (1) randomization arm, (2) lab/EKG collection schedule, and (3) transfusion regimen. When possible, the lab, EKG, and transfusion orders should be placed by a study team member. If verbal lab or transfusion orders are given by the

LSI to a resident or nurse, the order should be co-signed by the LSI according to the local facility's standard operating procedure. If the co-sign option is unavailable under Orders, the LSI or study team member must enter a CPRS note after the order has been placed indicating that the order was placed by resident/nurse at the LSI's request. If the note is entered by a study team member, the note must be co-signed by the LSI.

2. Follow-up Assessment

Follow-up assessments will be collected after participants are discharged from the hospital including 30- day and 90-day active follow-up assessments and one-year passive follow-up assessment.

a) Thirty Day Follow-up

Participants will be given an appointment for a clinic visit within one week after the 30 post-randomization day. Questions regarding symptoms related to MI, other cardiac events, stroke, pneumonia, and wound infection will be asked. If a participant has a readmission prior to the 30 day post-randomization time point, then the electronic medical record, will be reviewed to determine whether the reason for admission includes any of the complications that consist of the primary or other study endpoints, such as coronary revascularization or acute renal failure. If the participant has been admitted to a non-VA hospital, then complete records from this admission will be obtained from that hospital to document the reason for admission and whether any of the study endpoints have been developed which led to the readmission. The hospital records obtained will include History and Physical, all consultations, procedures, laboratory values, fluid cultures, copies of EKG and Echocardiography reports, as well as reports from all imaging studies performed, catheterization laboratory reports and operating room reports. To assure access to these records, release of information forms will have to be signed by the participant as part of the initial informed consent process. If the participant does not present for the follow up within two weeks from the anticipated appointment time, an electronic medical record review and phone call follow-up will be performed and focused questions will be asked, to identify the occurrence of any of the endpoints. Questions about interval readmission will also be asked at the follow up visit/call.

b) Ninety Day Follow-up

Participants will be given a clinic appointment within two weeks after the 90th post-randomization day. Questions regarding symptoms related to cardiac events, stroke, infectious complications will be asked as described above for the 30-day post-randomization follow up. If participants are unable to make the clinic visit within two weeks of the assigned appointment then an electronic medical record review and phone call follow-up will be performed as described above. Readmissions since previous follow-up will also be investigated with similar series of actions as with the 30 day post-randomization follow-up. Pertinent laboratory values (creatinine, troponin), EKG results, cardiac catheterization reports and operating room reports since the previous visit will be

reviewed in the electronic medical record to ascertain the presence of coronary revascularization, stroke, MI, or acute renal failure.

c) One Year Follow-up

This will be follow up performed by trained staff from the Chair's office who will call all study participants at twelve months after randomization to ascertain vital status. The CSPCC will generate listings of participants due for follow-up which will be sent to the Chairman's personnel responsible for conducting the telephone interviews. Follow-up data will be obtained by study staff. This removes the need for personal identifying information to be maintained at the individual sites or the CSPCC and helps to protect participant confidentiality. Furthermore, chart reviews using the CAPRI/VistaWeb/JLV system will be performed as a participant's death and the date of death are typically documented in the electronic medical record. Access to the national electronic health record will be requested. The VHA Death Ascertainment File (DAF) will be used to assess the one year vital status of those participants discharged alive from the hospital for whom vital status cannot be determined. Social Security number will be used to obtain the patient identifier PatientICN, which will be necessary for linkage to the DAF. We will request DAF data for all participants that have been randomized in the study. All additional deaths identified through the DAF will be reported by study staff to the CSPCC staff in an electronic file.

D. Missed Visits and Termination

1. Missed Visits

If the subject fails to present to the clinic for follow-up visit, the site coordinator at the site will call the participant within 10 days to inquire about the reason for the missed visit and to reschedule the participant's appointment as soon as possible. If the participant still refuses to come for a clinic visit, the site coordinator will complete as much of the assessment as possible on the phone and using information from the electronic medical records. We anticipate issues with no-show for clinic visits to be minimal, as standard of care entails that participants need to present for frequent clinic visits after the major operations included in this study. Missed visits will be documented. The Site Coordinator will maintain a phone log that will include date, time, phone number called, reason for the missed visit, rescheduled date of clinic appointment, and/or reason for visit refusal.

2. Termination

The active follow up period for study purposes will be up to 90 days after randomization. If the participant refuses to continue participation during active follow up, his or her participation in the study will be be terminated. All participants who complete the active follow-up phase of the study will be followed up to one year by the Chair's Office to assess mortality using a combination of phone call follow-up, search of the DAF, or electronic medical record

assessment. If a participant declines to participate in long term follow up then one year mortality data for this participant will not be collected. Given that the one year follow up is passive and does not involve any participant action we do not anticipate this to become a major issue.

X. TRANSFUSION STRATEGIES

Participants will be randomized to a liberal (transfuse if Hb <10 gm/dl) or restrictive (transfuse if Hb <7gm/dl) transfusion groups. Transfusion will be administered in order to maintain Hb just above the aforementioned thresholds for the index hospital stay or up to 30 days after randomization, whatever comes first. A participant must be randomized within 24-hrs of the first postoperative Hb falling below 10 gm/dl. It is strongly recommended that the transfusion treatment is initiated as soon as possible after and no longer than 24 hours from identifying a protocol-required transfusion Hb threshold.Transfusions will be administered according to the following scheme.

A. Liberal group (transfusion trigger: Hb < 10 gm/dl)

i. If Hb < 7.5 gm/dl transfuse three units PRBCs, then check Hb. Based on the return Hb value, follow the transfusion protocol (steps i, ii, or iii) until Hb $\geq$ 10.

ii. If 7.5 $\leq$ Hb < 8.5 gm/dl transfuse two units PRBCs, then check Hb. Based on the return Hb value, follow the transfusion protocol (steps i, ii, or iii) until Hb $\geq$ 10.

iii. If Hb $\geq$ 8.5 gm/dl transfuse one unit PRBCs, then check Hb. Based on the return Hb value, follow the transfusion protocol (steps i, ii, or iii) until Hb $\geq$ 10.

B. Restrictive group (transfusion trigger: Hb < 7 gm/dl)

i. If Hb < 5.5 gm/dl transfuse of two units PRBCs, then check Hb. Based on the return Hb value, follow the transfusion protocol (steps i, or ii) until Hb $\geq$ 7.

ii. If 5.5 $\leq$ Hb < 7 gm/dl transfuse one unit PRBCs, then check Hb. Based on the return Hb value, follow the transfusion protocol (steps i, or ii) until Hb $\geq$ 7.

If during the course of the initial transfusions, any routine, non-protocol required hemoglobin check shows that Hb is past the target threshold prior to administering the total number of units indicated by the protocol, transfusion may be stopped. (example: participant assigned to the Liberal arm and has Hb less than 7.5 is, per protocol, to receive three units of PRBCs. If after the second unit, a Hb check reveals Hb greater than or equal to 10, then a third unit of PRBC is not necessary.)

For Hb values that are suspected to be incorrect (i.e., artificially low or high in the context of the participant's clinical setting), order a repeat Hb within 6 hrs. of last lab to confirm values prior to initiating transfusion.

A participant in either group may be transfused at any time without an Hb level if there is evidence of rapid bleeding (e.g. brisk gastrointestinal bleeding or suspected intraabdominal bleeding after major aortic repair) and the physician believes emergency transfusion is needed.

Furthermore, if a participant develops signs or symptoms of a possible transfusion reaction, which are estimated to occur in approximately 1% of transfused patients, the transfusion will be stopped immediately and hospital policies must be followed with respect to reporting of blood transfusions and obtaining any applicable required blood and/or urine specimens for hospital testing. The transfusion strategy protocol may be reinstituted with a different unit of blood after the participant's condition has stabilized or if it is determined that the participant's signs or symptoms were probably not related to a possible blood transfusion. In the uncommon event that more than ¾ of a unit of blood is transfused prior to halting of the transfusion, then the ¾ of a unit may be considered a full unit of blood. A different unit of blood need not be transfused to fulfill the initial 1 unit requirement. The transfusion protocol may be continued as required.

If a participant experiences a myocardial infarction after being randomized to the transfusion protocol, the site investigators may either continue the participant's study assignment to the transfusion protocol or elect not to follow the participant's assignment to the transfusion protocol without removing the participant from the study. It is recommended that these participants continue on the transfusion protocol if randomized to that treatment, but the decision will be made by the site investigator and the participant's attending physician. This modification is made to reflect the lack of high level empirical evidence regarding the optimal transfusion threshold after patients experience a myocardial infarction.

Immediately following randomization, study personnel will place a label on the participant's room indicating that the patient is part of a transfusion study. The purpose of this label will be to remind housestaff that this is a study patient and that the Site Investigator needs to be contacted prior to making any transfusion decisions. The Site Investigator along with the Study Coordinator will be in charge of implementing the treatment protocol during work hours. On nights and weekends when Study Coordinator is not available then implementation of the protocol will be the responsibility of the Site Investigator(s). For patients who are in the Intensive Care Unit postoperatively special circumstances may arise, as care in ICU setting is sometimes provided by a group of intensivists in some hospitals. To facilitate study execution in these facilities, every effort will be made to designate an ICU attending surgeon as Site Investigator. If this is not feasible, then the intensivist team of physicians will be educated with respect to the study, and arrangements will be made for the Site Investigators to make the transfusion decisions in the randomized patients.

Participant Hb, creatinine, and troponin levels will be collected on days 1, 2, 3, 4, and 7 post-randomization or discharge (whatever is shortest). EKG will be performed on days 1 and 4 after randomization. If a participant is discharged prior to post-randomization day 4, EKG will be obtained at discharge. Results on Hb (standard of care/per transfusion protocol requirements), creatinine, troponin, and EKG performed at other time points will also be collected until discharge as supporting documentation for endpoint adjudication. If available at the institution, CK-MB will also be collected (not required).

Urine output will also be monitored in patients admitted to the Intensive Care Unit and it will be reviewed daily by the Study Coordinator. If the patient has anuria for more than 12 hours, or has urine output less than 0.3 ml/Kg/hr for more than 24 hours then the urine output will be documented as evidence for the development of ARF.

Hemoglobin and transfusion record**:** We will record the number of blood transfusions during the preoperative, intraoperative, and postoperative time periods. The protocol requires that Hb levels be measured on day of randomization, days 1,2,3, and 4 after randomization as well as on day 7 if the participant remains in the hospital. Hb measurements, performed as standard clinical practice, will also be recorded. The Site Coordinator will record information on a) preoperative, intra-operative, and postoperative transfusions, and b) Pre- and post-randomization Hb levels. Information on Hb levels and transfusions will be obtained by contacting the hospital laboratory directly or from the chart. Information on transfusions will be obtained from the chart and the blood bank.

XI. MONITORING AND REPORTING SERIOUS ADVERSE EVENTS

A. Importance of Serious Adverse Event Reporting

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence, thereby allowing: a) protection of safety of study participants, b) a greater understanding of the overall safety profile of the study treatments and therapeutic modalities, c) improvements in study design or procedures, and d) compliance with regulatory requirements.

B. Role of the Local Site Investigator in Serious Adverse Event Monitoring

The local site investigator, as well as other site personnel, shall be personally responsible for the following requirements:

1. Closely monitoring all study participants for new SAEs;
2. Reviewing the accuracy and completeness of all SAEs reports;
3. Completion of all SAE case report forms as required by this protocol and further described in the study Operations Manual;
4. Complying with Cooperative Studies Program (CSP) policies for reporting SAEs;
5. Knowing and complying with the VA Central IRB (CIRB) (accessible at http://www.research.va.gov/vacentralirb/) and VHA Handbook 1058.01 Research Reporting Compliance Requirements section 7.a, 7.b and 7.c (accessible at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=2463) reporting requirements for unanticipated problems. Education on the responsibility of site study staff at each participating site to know and comply with these requirements will be a component of the study kickoff meeting, reinforced at study annual meetings, and on periodic conference calls. Questions about managing or reporting of serious adverse events will be directly addressed by the Study Pharmacist at the CSPCRPCC, CSPCC or the Quality Assurance Nurse (QAN) at the CSPCC. These requirements, however, do not eliminate the need for investigators to report SAEs to the CSP Sponsor as per the study's Operations Manual, and;
6. Complying with local Research & Development Committee (R&DC) policies and CIRB of record policies for reporting SAEs;

7. Closely monitoring research participants during their study participation at each follow-up visit for any new SAEs and for follow-up of previously reported SAEs
8. Providing SAE follow-up information at least every 30 calendar days or sooner if new information becomes available until the SAE has resolved or is stable with no changes anticipated in the future.
9. Notifying the CIRB or record and local R&DC of safety issues reported to the investigator by the Study Sponsor (CSP).

C. Definitions

1. Serious Adverse Event

Serious adverse events are defined by the ICH for Clinical Safety Data Management (ICH-E2A), the Food and Drug Administration (21CFR312.32 and CSP Global SOP 3.6, as any untoward medical occurrence that:

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect, or
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical, surgical, behavioral, social or other intervention to prevent such an outcome.

2. Relatedness

Relatedness involves an assessment of the degree of causality (attributability) between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness. The assessment provided by the site investigator is part of the information used by the sponsor to determine if the adverse event presents a patient safety concern and/or requires regulatory reporting. Pursuant to CSP Global SOP 3.6, a SAE is deemed to be associated with the use of a study drug/device if “there is a reasonable possibility that the experience may have been caused by the drug/device or by participation in the trial.” Thus, all SAEs with a reasonable causal relationship to the investigational treatment should be considered “possibly related” or “related.” A definite relationship does not need to be established but there must be some evidence to suggest a causal relationship between the investigational treatment and the adverse event (21 CFR 312.32). The following levels of relatedness will be used in this trial:

- Not attributed to a study intervention
- Possibly attributed to a study intervention
- Attributed to a study intervention

D. Collection of Safety Information

Given the large number of comorbidities expected in the study population and the high-risk operative procedures these patients will be undergoing, it is anticipated that a large number of AEs will be observed, most of which will not be related to the study intervention. For this reason, the study will only collect reports of Serious Adverse Events (SAEs).

All SAEs, whether related or unrelated to the treatment interventions, will be recorded and reported in an expedited fashion. Assessment of relatedness for SAEs is described above. Unexpected serious adverse events that are attributed or possibly attributed to a study intervention will be managed as provided in CSP Global SOP 3.6.

Directions on how to complete the Serious Adverse Event Form will be detailed in the Operations Manual. Sites are required to report each SAE to the Sponsor within 3 calendar days from the time the site investigator becomes aware of it. The PCC Study Pharmacist will complete a safety and regulatory review of all SAEs. All investigators will be notified of any new hazards or other trends involving patient safety as provided in Global SOP 5.3.

Active monitoring of reportable SAEs will begin as soon as randomization is complete and will end at 90 days after randomization or termination. The treatment plan includes follow-up outpatient visits of all participants for 3 months after randomization.

1. Expedited Reporting of Serious Adverse Events

All SAEs require prompt reporting to the CSP Coordinating Center and CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) within 3 calendar days of the site investigator becoming aware of the event. The Pharmacist at the CSPCRPCC is responsible for evaluating all SAEs for participant safety concerns and/or regulatory reporting. The Pharmacist will consult with the Chairman's office during the review process, as necessary. The CSPCPRCC maintains a database of serious events for evaluation, by using the Medical Dictionary for Regulatory Activities (MedDRA) for coding and trending. Periodic summaries will be provided to the Data Monitoring Committee, the Study Chairman's office and Executive Committee (as necessary). Events that are determined to be serious, unexpected, and related to the study treatments will be reported to the site investigators, CIRB, and to the VA Cooperative Studies Program Central Office.

SAE Forms will be sent to the Perry Point CSPCC as directed. The CSPCRPCC will also have access to the information on the SAE Forms.

2. SAE Follow-up Reporting

If additional information is required the CSPCC or CSPCRPCC will fax or email a request to the site personnel reporting the SAE. The site should handle requests for SAE follow-up information in the same prompt manner that original SAE reports are handled. Serious adverse events should be followed to resolution, stabilization, or the participant's last active study contact , whichever occurs first. If an SAE is still ongoing by the time the SAE Form is submitted to the Perry Point

CSPCC, complete an SAE Follow-up Form every 30 days until the SAE is resolved or stabilized. SAE Follow-up Forms will be sent to the Perry Point CSPCC as directed. The CSPCRPCC will also have access to the information on the follow-up SAE Forms.

It is the responsibility of the site investigator / coordinator at each participating site to know and comply with the SAE reporting requirements of the VA CIRB.

The CSPCRPCC is responsible, in conjunction with the CSPCC, for coding study safety data into the MedDRA (Medical Dictionary for Regulatory Affairs) Dictionary and creating event tabulations. The study biostatistician will present a summary of those events to the data monitoring committee (DMC) on a schedule set by the DMC. The DMC will recommend to the CSRD Director whether the study should continue or be stopped for safety reasons. Summary reports from the DMC will be provided to each site for their records.

Unexpected SAEs will be reported to the Study Chairs' Office. The Study Chairs and the CSPCC Directors will report SAEs that are determined to be both related to the investigative treatment and unexpected to the CSRD Director and site investigators after review.

E. Risks to participant

- *Risks related to transfusions:* Known risks related to blood transfusions include, but are not limited to, infection or irritation where the needle is placed, temporary reaction such as fever, chills, or skin rashes. Other rare but more serious complications may occur such as allergic reactions. Symptoms of allergic reactions include anxiety, chest and/or back pain, trouble breathing, fever, chills, flushing, and clammy skin, a quick pulse, and/or nausea (feeling sick to the stomach). Other rare but more serious complications include: heart failure due to fluid overload, acute pulmonary edema (fluid leaking into the lungs), shock, or death. Transfusions of blood involves a small risk of transmission of diseases such as Hepatitis B (1 in 137,000), Hepatitis C (1 in 1,000,000), and HIV/AIDS (1 in 1,900,000). There is also a small risk of bacterial infection when blood products are transfused.

  The risk associated with receiving too much blood is heart failure due to fluid overload and an iron overload. Getting too many blood transfusions can cause too much iron to build up in the blood. People who have a blood disorder like thalassemia, which requires multiple transfusions, are at risk for iron overload. Iron overload can damage the liver, heart, and other parts of the body.

  Receiving too little blood may reduce the body's ability to deliver oxygen to organs and other vital systems. Without oxygen, critical functions of the body will be interrupted and/or damaged.

  Acute immune hemolytic reaction is very serious, but also very rare. It occurs if the blood type received during a transfusion does not match or work with the recipient's

blood type. The body attacks the new red blood cells, which then produce substances that harm the kidneys. Symptoms of acute immune hemolytic reaction include chills, fever, nausea, pain in the chest or back, and dark urine.

Delayed hemolytic reaction is a much slower version of acute immune hemolytic reaction. The body destroys red blood cells so slowly that the problem can go unnoticed until the red blood cell level is very low. Both acute and delayed hemolytic reactions are more common in patients who have had previous transfusions.

Graft-versus-host disease (GVHD) is a condition in which white blood cells in the new blood attack tissues. GVHD usually is fatal. People how have weakened immune systems are the most likely to get GVHD. Symptoms start within a month of the blood transfusion. They include fever, rash, and diarrhea. To protect against GVHD, people who have weakened immune systems receive blood that has been treated so the white blood cells can't cause GVHD.

- *Risks related to venipunctures needed for the blood draw procedure:* temporary discomfort, slight pain, weakness, dizziness, or bruising. Rarely, a blood clot may form in the vein that was used for the blood draw. The blood clot may cause serious discomfort that may require a short period of anti-inflammatory medications or to fully resolve. The blood clot may also lead to infection.

- *Risks related to EKGs:* skin irritation due to the pads that are placed on the skin and some risk of pain when the pads are removed from the skin

- *Risks related to the loss of confidentiality:* minimal risk for the loss of confidentiality.

In addition to the risks identified above, there may be unknown risks associated with these procedures

F. Benefits for study

Veterans will be notified that there are no benefits from taking part in this research study. All participants will receive $25 per outpatient clinic visit or phone call visit as compensation for travel and meal related expenses.

XII. QUALITY CONTROL PROCEDURES

A. Standardization/Validation of Measurements

Prior to the start of the study recruitment, all of the site investigators and research coordinators will be provided with in-depth trainings on different aspects of the conduct of the study during a "kick-off" meeting to ensure proper understanding of the technical aspects of the protocol, to ensure uniformity in the completion and submission of the case report forms and to ensure uniformity in implementing and performing the study procedures.

Site investigators and research coordinators will also receive informed consent and study procedures training by the CSPCC staff during the kick-off meeting. CSPCC staff will provide training on study procedures including the use of the study SharePoint portal, data collection on the iDataFax platform, randomization and assessment schedules.

B. Participant Management

This research study will be conducted in full accordance with ethical principles of human research, including the provisions of the World Medical Association Declaration of Helsinki. All participants will be screened for study eligibility using the same inclusion/exclusion criteria as defined in this protocol. Those participants who qualify will be engaged in the study consent process by the clinical care team in collaboration with the research coordinator and led by the surgeon investigator. For those who agree to participate, local sites will adhere to their institution's established best clinical practices in the care of the participants with exception to allowing for randomization postoperatively once the participant's Hb falls below 10 gm/dl. Participants will be followed throughout their hospital stay for research data collection including any serious adverse events (e.g. major adverse cardiac events). Usual post-operative care will follow institutional standards

Participants will be encouraged to seek medical attention as instructed upon discharge from the hospital. Throughout the duration of the study participation, the participant will be encouraged to maintain a point of contact with the local site investigator and the study coordinator for research related activities and questions. The study team at each site will maintain a dedicated point of contact for all participants seeking information during their study participation. The study coordinator at each site will communicate any necessary medical information to the surgeon investigator and the clinical care team.

C. Protocol Violations

Any protocol violation will be reported immediately to the Chairman's office and the Perry Point CSPCC. Each of these groups then reserves the right to forward notification, as required by local policy and regulation. Protocol violations will be forwarded to the VA central IRB based upon guidelines provided. Approved instances for transfusion strategy halting include: transfusion of a participant regardless of group (restrictive or liberal) assignment in case of rapid bleeding; stopping transfusion due to adverse reactions to blood transfusion; and halting transfusion protocol, at the attending surgeon's discretion, if the participant develops a post-randomization MI. Any other deviation from the protocol will be considered a protocol violation.

D. Plans to be implemented if recruitment goals are not met

If recruitment has fallen short of anticipated goals, the following will be considered to improve participant recruitment:

- Eligibility criteria will be reassessed to determine if there are any alterations in inclusion/exclusion criteria that could be made to increase recruitment. A conference call/meeting of the Executive Committee with local site investigators will occur to discuss any change in eligibility criteria.

- We will expand the study population to include patient undergoing high-yield, common orthopedic operations, such as hip and knee replacement.
- Additional sites will be considered, if needed.

E. Site Performance Monitoring

1. Monitoring Medical Center Performance

Strict adherence to the protocol will be expected of every participating center and monitored by the DMC and the Executive Committee. Documentation of protocol noncompliance will be required, and medical centers with repeated protocol noncompliance may be subject to termination.

If a participating investigator feels that adherence to the protocol will in any way be detrimental to a particular participant's health and well-being, the interest of the participant must take precedence. Those instances may arise during the course of usual patient care, but the participating investigator will need to provide justification for the actions and the circumstances that led to noncompliance.

By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Cooperative Studies Program and personnel listed above. However, the Research and Development (R&D) Committee and the IRB of record may require the participating investigator to submit annual and final progress reports concerning the status of the study at the medical center for local monitoring purposes.

2. Guidelines for Special Attention, Probation or Early Termination of a Participating Site

During the course of a study, it may be necessary to critically review participating medical centers on recruitment and protocol compliance measures. Such actions will be a collaborative effort between study leadership and an individual site.

Early termination is usually based on recommendations from the Executive Committee and/or the Data Monitoring Committee. Often, it reflects inadequate participant intake or serious non-adherence to the protocol or with Good Clinical Practices (GCP) Guidelines. This action will always in the best interests of the study and study participants and does not necessarily imply poor performance on the part of the SI or the medical center. Termination will be conducted per CSP policies. All site termination decisions will have the prior approval of the CSPCC Director and the Director, CSP.

3. Premature Termination of the Study

The director, CSP, can terminate a cooperative study before completion. The DMC makes recommendations as to whether the study should continue or be terminated. The decision to terminate a study prematurely is a complex one involving many factors. The DMC may consider the following circumstances as grounds for early termination:

a. If participant accrual falls far below that which is predicted (e.g., 75% of expected accrual), it will be necessary to reassess the study design and the potential value of its continuation.
b. If participant accrual far exceeds the predicted, this study could be completed at an earlier date.
c. If serious adverse events or deaths are noted to be excessive in either treatment group.
d. If interim analyses indicate a trend in the data which is unlikely to change prior to study completion.
e. If, during interim analyses on the primary end point, the significance level crosses the efficacy boundary established by the DMC.

4. Recruitment Issues

The study chair and the study biostatistician will monitor the intake rate and operational aspects of the study. Participating medical centers that do not maintain adequate participant intake may be terminated from the study. The Executive Committee may also recommend the discontinuation of recruitment at a center with the concurrence of the CSPCC Director and Director, CSP.

The leadership team along with potential input from the Executive Committee and/or DMC will determine the feasibility and necessity of excluding participating medical centers. Other options that may be considered include: probation with a detailed action plan, inclusion of new medical centers, minor modifications to the inclusion/exclusion criteria, or extending the recruitment period.

If a participating medical center is placed on probation, the study chair will confer with the site personnel and may visit the site, if necessary, to help improve the rate of recruitment. If there is no improvement in accrual during the probation period, the site may be subject to reduced funding or possible discontinuation as a study site. To plan for the possible termination of one or more sites and the addition of any new sites, back-up sites with CIRB approval may be identified prior to study initiation to minimize the delay in adding a new site. Actions to discontinue a site will occur with the concurrence of the CSPCC Director and CSP Director and/or the Executive Committee. If a site is terminated from the trial, resources will be reallocated to other medical centers or used to start up a back-up site.

5. Non-adherence to the protocol and/or Good Clinical Practice (GCP) Guidelines

Strict adherence to the protocol and GCP guidelines will be expected of every participating medical center and monitored by the DMC, the Executive Committee, and the Study Group. Documentation of protocol deviations will be required. Medical

centers with repeated major protocol non-compliance or repeated failures to follow GCP Guidelines will be recommended for termination to the DMC, the CSPCC Director, and the Director, CSP. If a participating investigator feels that adherence to the protocol may result in an apparent immediate hazard to the participant, the interest of the participant must take precedence.

Protocol violations must be immediately reported to the CSPCC on the appropriate case report form and may require reporting to the Central IRB of record to ensure immediate hazard to the participant did not occur.

XIII. DATA MANAGEMENT

A. Data Collection and Data Entry

Data management will be performed by the VA CSPCC Perry Point, MD using DataFax data management software. The CSPCC will have overall responsibility for the data at the end of the study.

All data will be collected at the study sites on source documents, which will be entered at the site into paper CRFs. The blank CRFs will be supplied by the CSPCC. CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the study operations manual. The Site Investigator is responsible for maintaining accurate, complete and up-to-date records for each participant. The Site Investigator is also responsible for maintaining any source documentation related to the study.

Completed CRFs will be submitted by site personnel on a regular basis to the iDataFax system at the CSPCC. iDataFax provides the options for site personnel to enter data elements into local study computer linked to CSPCC database as well as to fax the CRF to the CSPCC, and allows the clinical centers to retain the original CRF and source documents while providing an image to the CSPCC. Data entered into the database or faxed within the image are then checked for accuracy/completeness and entered into the study's database using iDataFax software. Data received at the CSPCC will be reviewed, verified and edited before being entered into the main study database. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the clinical site for a response. Sites will resolve data inconsistencies and errors before resending the corrected CRFs to the CSPCC. All corrections and changes to the data will be reviewed before being entered into the main study database. The participating sites will receive reports at least monthly regarding the quality and quantity of data submitted to the CSPCC.

Site investigators agree to routine data audits by the staff of the VA CSP monitoring unit, as well as by the CSPCC staff. The VA CSP monitors will routinely visit each site to assure that data submitted on the appropriate forms are in agreement with source documents at the sites. They will also verify that participant informed consent for study participation has been obtained and documented in the participant's progress notes, all essential documents required by GCP regulations are on file, and sites are conducting the study according to the research protocol.

Any inconsistencies will be resolved, and any changes to the data forms will be made using established the CSPCC procedures.

When the study is completed and all data have been entered into the database and the database has been checked for quality and is locked, the CSPCC statisticians will perform statistical analyses of the data in accordance with the Statistical Analysis Plan (SAP). Periodically, during the study, the CSPCC will prepare various summary reports of the data so that progress of the study can be monitored. These reports will be prepared for the Data Monitoring Committee (DMC) and other committees, as appropriate.

B. Archiving Study Data

Study documentation includes all paper CRFs, data clarification forms, source documents, monitoring logs and appointment schedules, investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, etc.).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. Thus, source documents include, but are not limited to clinical reports, participant completed assessments, progress notes, hospital charts or pharmacy records and any other reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Research records for all study participants are to be maintained by the investigator in accordance with the VA record control schedule until notified by the CSPCC. These records are to be maintained in compliance with IRB, State and Federal requirements, whichever is longest. It is the investigator's responsibility to retain copies of the completed CRFs until notified in writing by the CSPCC that they can be destroyed. In all instances, the site must get permission from the CSPCC prior to disposition of any study documentation and materials.

XIV. DATA SECURITY PLANS

The clinical data management system to be used in this study will be fully compliant with US Federal regulations regarding electronic web-based data capture systems established by the Food and Drug Administration under 21 CFR 11. Data entered directly into the database provides the official clinical record for data collection. Source documentation is handled in the same manner as a paper-based system. All paper-based records will be kept in locked file cabinets.

The servers housing the study databases will be located at a secure VA facility and housed behind the VA firewall on VA owned and maintained servers. The information housed within the data management system will have the same level of security as all forms of VA protected and/or

highly sensitive information. The system will be monitored to ensure that all applicable VA regulations and directives are strictly followed.

Access to the study data is restricted by the CSPCC to properly-credentialed research staff who have completed required VA security trainings. An individual site's study staff may only see the data for participants from their site. Only CSP-approved individuals (such as: staff at the study site, CSPCC, and CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC)) will have access to the personal health information (PHI) of study participants. In addition to the VA CSP, the Study Chair's Office will have access to identifiable information so that they can call the study participant one year after their surgery. Identifiable information shared with the Chair's Office will include: SSNs, phone numbers, and names. The Study Chair's Office is located at the VA New York Harbor Health Care System in Brooklyn, NY.

Research data will only be stored on secure VA servers within the VA firewall. The data will be coded with a unique study identifier for each participant and stored using that study identifier. Identifiable information will be collected for participant tracking and safety purposes, and to collect health care usage and cost data. Coded clinical data will be stored separately from the participant's personal identifying information (i.e., participant's name, contact information, and real SSN). Access to the cross-walk file linking the participant's identifiers and their study data will be restricted to the clinical site and to the study staff at the CSPCC.

Microsoft SharePoint will be used to store study documents and as an alternative solution to transmit data from study sites to the CSPCC. Security protocols for SharePoint will be in place:

- Access and Permissions: Site Specific permissions, document library access will be limited to the appropriate personnel.
- Semi-Annual Audit of Permissions: the SharePoint Administrator maintains an access log. All access is granted by the SharePoint administrator/site owner and granted based on approved requests.

In case of improper use or disclosure of study data, the facility's ISO and Privacy Officer, and the individual's direct supervisor will be notified immediately per VA Directive and Handbook 6500. Records will be destroyed in accordance with the VHA Records Control Schedule and VHA Handbook 1200.05.

The system will utilize technologies to protect data during transmission. All of these technologies will meet or exceed current VA standards for data transfer. The data management system will use secure socket layer technology and FIPS 140-2 compliant encryption algorithms to ensure data are not vulnerable during transport. All data will be stored within the VA firewall and password protected at all times. Hard copy data will be sent via a traceable mail system (e.g. UPS), courier, or secure fax.

Quality control checks and clinical monitoring will enable the CSPCC to examine the database and the clinical sites to ensure data have not been improperly used or accessed. Audit trails and access logs compliant with 21 CFR part 11 will be checked routinely, and clinical monitors will provide continuing education on GCP and check clinical site operations for violations of data security policies and best practices.

XV. GOOD CLINICAL PRACTICES

A. Good Clinical Practices (GCP)

This trial will be conducted in compliance with Good Clinical Practices (GCP) regulations. The intent of these regulations is to safeguard participants' welfare and assure the validity of data resulting from the clinical research. The VA CSP will assist Local Site Investigators (LSIs) in complying with GCP requirements through its Site Monitoring, Auditing and Resource Team (SMART) based in Albuquerque, NM. SMART serves as the Quality Assurance arm of CSP for GCP compliance. SMART will provide training, manuals and materials to assist study personnel in organizing study files and will be available throughout the trial to advise and assist LSIs regarding GCP issues.

Monitoring of sites participating in the trial will be executed according to VA CSP guidelines. SMART will conduct initiation visits at each site soon after the first participant is enrolled. Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART.

Independent routine audits will be conducted at one or more sites per year as determined by SMART. For-cause audits will be conducted as requested by study leadership or CSP Central Office. These audits may be scheduled or unannounced.

The purpose of these site visits is to encourage and assess compliance with Good Clinical Practice requirements. Monitors/Auditors will examine participant study files including source documents in both the clinic files and the participants' official VA medical records and will also review regulatory/essential documents such as correspondence with the VA's Central IRB and Sponsor (CSP). Areas of particular concern will be participant informed consent issues, protocol adherence, safety monitoring, VA's Central IRB reviews and approvals, regulatory documents, participant records, drug accountability and investigator supervision and involvement in the trial. Reports will be prepared following the visit and sent to the LSI. In addition, the CSPCC in collaboration with SMART will monitor study sites remotely through weekly reports, data queries and SC/LSI conference calls.

B. GCP Training

All primary Site Investigators and primary Study Coordinators will be required to complete CSP SMART GCP training and will also maintain ORD required training by taking the on-line CITI training (https://www.tms.va.gov) or ORD equivalent every three years for the duration of the study. All other study personnel must take the on-line CITI training or ORD equivalent prior to assuming their role on the study and then every two years thereafter for the duration of the study. If additional sites are added or there is turnover in personnel, any new primary SI or primary SC are to satisfy the same requirements as delineated above for the primary SI or primary SC. Written verification of GCP/HSP training of study site personnel will be submitted to the CSPCC prior to the start of participant recruitment at each site.

C. Summary of Monitoring and Auditing Plans

a. Monitoring Visits
   (1) Initiation visits at each site soon after sites randomize their first few participants
   (2) Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART.

b. Audits
   (1) Routine audits – independent site visits to one or more sites per year as determined by SMART.
   (2) For-Cause audits –independent audit of a site as requested by study leadership or CSP Central Office.
   (3) Audits may be scheduled or unannounced.

XVI. BIOSTATISTICAL CONSIDERATIONS

A. Expected Treatment Effects

In order to estimate 90 day composite endpoint rate (defined in Section V) after surgical interventions in the VA population, we conducted an analysis of Vascular and General Surgery operations identical to those targeted in the proposed trial as described in pages 5-7. Data of 171,357 VA patients who underwent these vascular or general procedures and had available nadir Hb level from the Corporate Data Warehouse (CDW) database was used for this analysis. We anticipate in the proposed trial the nadir Hb in the restrictive transfusion group to range between 6-9 gm/dl (transfusion trigger Hb < 7 gm/dl). Our database review revealed that 29.8% out of 25,343 patients who were at high cardiac risk and had nadir postoperative Hb at this range developed the composite endpoint of death, MI, acute renal failure, or coronary revascularization within 90 days from the index operation. The breakdown of event rates for the individual components of the composite endpoint is shown in Table 2 . Based on the analysis, a baseline event rate of 30% for the composite endpoint is expected in the restrictive group.

B. Sample Size Calculation and Power Analysis

The sample size estimation and power analysis are based on the hypothesis testing of the primary composite endpoint, which is the most important measure proposed in the study. According to the analysis of event rates outlined in the previous section, we assume that 30% rate for the primary endpoint can be anticipated in the restrictive transfusion group. We also assume a 25% reduction or 22.5% event rate in the liberal group. The sample size for the study is estimated based on a superiority trial design. To detect the expected 7.5 percentage point difference or 25% reduction, a sample size of 1444 will be required at 90% power, 5% type-I error rate and with a two-sided test (TABLE 3). Assuming 5% dropout rate, then 1520 participants (or 760/group) will be needed to achieve the desired testing power.

TABLE 3 Sample Size Estimation and Power Analysis

90 Day Composite Endpoint (%)				Power (%)			
Liberal	**Restrictive**	**Difference**	**Percent Difference**	**75**	**80**	**85**	**90**
17.50	25.00	7.50	30.0	826	932	1066	1248
18.75	25.00	6.25	25.0	1214	1372	1570	1836
20.00	25.00	5.00	20.0	1936	2188	2502	2928
21.00	30.00	9.00	30.0	650	734	840	982
22.50	**30.00**	**7.50**	**25.0**	**954**	**1080**	**1234**	**1444**
24.00	30.00	6.00	20.0	1520	1718	1964	2298
24.50	35.00	10.50	30.0	526	594	678	794
26.25	35.00	8.75	25.0	770	870	994	1164
28.00	35.00	7.00	20.0	1222	1382	1580	1848

C. Duration of Study and Number of Participating Sites

To calculate the expected study duration and resources, we assume that the recruitment rate will be half of what we anticipate. Under this assumption, various scenarios were examined in order to identify an optimal combination between the number of sites, the study duration (which includes recruitment period and follow-up period) and the estimated budget. By conducting the study with 15 sites and 3 participants/month/site rate of recruitment, the recruitment period was found to be approximately four years. This will be followed by three months of active follow-up and 9 months of passive follow up for the last subject randomized into the study. Thus, the study duration including start-up, will be five years.

D. Feasibility Phase

In order to confirm the hypothesized control proportion for the primary outcome, to determine the feasibility of recruiting average 3 participants per site per month, and to assess other operational aspects of the study, a feasibility phase has been built into this study. The planned duration of the feasibility phase of the study is one year and will include 3 NODES sites (Houston, Minneapolis, and Dallas VA Medical Centers) and five additional sites with existing research infrastructure and high expected recruitment rates (Cleveland, Buffalo, Tampa, Gainsville, and Little Rock VA Medical Centers).

During the feasibility phase, several site start-up activities and operational aspects of the study will be examined. These activities will include the hiring of site personnel (including classification of position descriptions, position announcements and recruitment), the methods by which site staff are trained on data collection and management activities, the practicality of consent, randomization and attrition (drop-out) rates. The lessons learned during this phase will be implemented during activation of the remaining 7 participating sites.

Recruitment rates at the eight active sites will be closely monitored during this phase. The initial eight sites are each expected to enroll 36 participants in the first year of the study, for a total of 288 participants at the end of the first year. The actual recruitment experience of the eight sites in the first year will be used to revise the projected recruitment rate for the remainder of the study and may lead to a lengthening or shortening of the total recruitment period, as appropriate. Measures to address unexpectedly low recruitment rates during this feasibility phase have been described on page 14. At the completion of the feasibility phase, the study will be moved to a continuation phase where the remaining 7 sites will be activated and the remaining participants (1232 participants) will be recruited and followed up.

E. Data Analysis Plan

The primary analysis will be performed to test the null hypothesis of no difference in composite outcome of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke between participants randomly assigned to a 10 gm/dl Hb transfusion strategy compared to participants assigned to 7 gm/dl transfusion strategy. If the null hypothesis is not rejected, a 95% confidence interval will be constructed about the difference observed to inform the medical community as to how large the difference is likely to be in either direction. All statistical tests will be two-sided and the primary outcome will be tested at 5% level of significance. SAS 9.4 or higher will be used to conduct all the statistical analyses. A variety of analytic methods will be used for the primary endpoint, secondary endpoints, tertiary endpoints and other analyses (TABLE 4).

1. Analysis Populations

Intent-to-Treat (ITT) – This population is defined as the population of participants who will be randomized to either of the transfusion strategy groups – Liberal or Restrictive. The participants will be categorized (in terms of their transfusion strategy assignment) based on their initial randomized group and will be included in analyses irrespective of their status – completer or drop out of the study before completion. The testing power for the primary endpoint is estimated as 90% in this population.

Modified Intent-to-Treat (mITT) – This population is defined as a subset of the ITT population that excludes randomized participants in a justified way, i.e, participants who are found to be ineligible (violating major inclusion/exclusion criteria), such as non-Veterans, previous participants of this trial.

No-Recent-Transfusion – This population is defined as a subset of the ITT population excluding the participants who will receive transfusion(s) within 30 days prior to or during the index operation, or after the index operation but before randomization.

Completers – This population includes all ITT participants who will complete all assessments in the hospital stay, as well as 30 day and 90 day follow-up.

Per Protocol – This population includes all ITT participants who will adhere to transfusion protocol in their assigned intervention groups.

Safety – This population includes all participants who will be randomized to either of the transfusion strategy groups – Liberal or Restrictive.

The primary analysis of the study will be performed on the primary endpoint on the ITT population. The secondary analyses will be performed on the secondary and tertiary endpoints on the ITT population, as well as the analyses performed on all the primary, secondary, and tertiary endpoints on the mITT, No-Recent-Tansfusion, Completers, and Per Protocol populations. SAE will be analyzed based on the Safety population.

2. Primary endpoint analysis

The primary study endpoint will be composite outcome of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke within 90 days from randomization. This outcome will be compared according to assigned transfusion strategy (analysis by intent to treat), using Pearson χ^2 test. The test for differences between transfusion strategies in the primary outcome will be conducted at an overall α-level of 0.05. Additional analysis will be conducted using logistic models to adjust for other clinical factors, such as age, RCRI, nadir Hb, and interaction terms. Logistic regression will be used for the primary endpoint (y = 1 if a composite outcome, otherwise y = 0) analysis with transfusion strategy group as the testing factor (x). The following covariates will be included in the model: age (z_1), RCRI (z_2), nadir Hb(z_3), site (z_4), and the interactions of testing factor with age (w_1), RCRI (w_2) and nadir Hb (w_3). Given the composite outcome probability $p=\Pr\left(y=1|x,z_1,z_2,z_3,z_4,w_1,w_2,w_3\right)$, the basic model is defined as follows:

$$Logit\left(p\right)=\ln\left(\frac{p}{1-p}\right)=\beta_0+\beta_1 x+\beta_2 z_1+\beta_3 z_2+\beta_4 z_3+\beta_5 z_4+\beta_6 w_1+\beta_7 w_2+\beta_8 w_3$$

Odds ratio and 95% confidence interval (CI) will be presented using SAS PROC GENMOD. If the coefficient for treatment effect is significant, then the null hypothesis will be rejected. Logistic models will be tested for goodness of fit. We will assess goodness-of-fit using the statistic -2 log likelihood, which has a chi-square distribution under the null hypothesis that all the explanatory variables in the model are zero. We will also consider the Akaike Information Criterion statistic and the Schwartz Criterion statistic, both of which adjust the -2 log likelihood for the number of items in the model. Models that show lack of fit will be reconsidered for the inclusion of additional variables or use of alternate models with assumptions that are better met by the study data. One alternate model if model fit is poor for logistic regression is a log-linear model.

3. Secondary endpoint analyses

Secondary endpoints included in the analysis are composite endpoints of infectious complications (wound infections, pneumonia, and sepsis) and cardiac complications (arrhythmia, CHF, exacerbation, and cardiac arrest), composite events of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke at 30 days, all-cause mortality at one year, and length of hospital stay. For the binary endpoints, the effect of transfusion strategy on these endpoints will be analyzed initially with a Pearson chi-square test and additional analysis will be performed by taking account of age, RCRI, nadir Hb, site ,and the

interaction terms using logistic regressions as described in the primary endpoint analysis. For the length of hospital stay, medians (interquartile ranges) will be presented and Wilcoxon test, a nonparametric method, will be used to compare the medians of the length of hospital stay between the two intervention groups. In addition, quantile regression will be used to test the effect of the intervention on the time until discharge from hospital adjusted for age, RCRI, nadir Hb and the interaction terms as described in the primary analysis. The test for differences between transfusion strategies in each secondary outcome will be conducted at an α-level of 0.01.

4. Tertiary endpoint analyses

Tertiary endpoints included in the analysis are individual components of the primary composite outcome of all-cause mortality, MI, coronary revascularization, acute renal failure, or post-randomization stroke at 90 days. All are considered as binary variables in the study, and the effect of transfusion strategy on these endpoints will be analyzed initially with a Pearson chi-square test. The test for differences between transfusion strategies in each tertiary outcome will be conducted at an α-level of 0.01. Additional analyses will be carried out by taking account of age, RCRI, nadir Hb and the interaction terms using logistic regressions as stated in the secondary endpoint analyses.

5. Other analyses

Baseline characteristics

Subject demographics and pre-surgical baseline characteristics will be summarized for each intervention group and for all participants (ITT and mITT). The subject demographics such as age, race, gender, ethnicity etc. and baseline test results such as Hb, albumin, troponin, creatinine, EKG, SBP/DBP, BMI, RCRI etc. will be analyzed. For continuous variables, the sample size, mean, median, SD, minimum, and maximum values will be calculated and tested either by Student t or Wilcoxon test depending on data distributions. For categorical variables, the number and percentage of participants by the intervention group will be tabulated and tested using Pearson chi-square test.

Disposition status

Subject disposition will be summarized for the ITT and mITT populations. The number and percentage of participants who completed or discontinued prematurely from the study by intervention group will be tabulated and tested using Pearson chi-square test. The number and percentage of participants who discontinued for each reason will be presented for each intervention group. The number and percentage of participants who completed or discontinued prematurely in each intervention group will also be displayed graphically.

Adherence

Participants who change transfusion strategy after randomization or have protocol violations will be identified as non-adherence to the intervention (ITT and mITT). The number and percentage of non-adherence participants will be summarized by intervention group and tested using Pearson chi-square test.

Age of blood in relation to 90 day composite endpoint, wound infection, and pneumonia

Analyses will be conducted of the associations between characteristics of transfused blood and three outcome measures (90 day composite endpoint, wound infection, and pneumonia). Current data collection plans call for blood expiration dates and the age of each unit of blood transfused will be calculated. Logistic regression models will be fitted to test for association between these outcomes and age of blood transfused (entered in different models as oldest unit transfused or as mean age of all units transfused). The analyses will be adjusted for age, RCRI, nadir Hb, site, and the transfusion intervention. The test for differences of these outcomes will be conducted at an α-level of 0.01. The analyses will be done on the ITT, mITT, No-Recent-Tansfusion, Completers, and Per Protocol populations.

Time-to-event analysis for primary and major secondary endpoints

Survival analysis techniques will be used to analyze the time-to-event data for the primary and major secondary endpoints. Kaplan-Meier analysis will be used to estimate the survival (not experiencing event) over time in the two intervention groups and a log-rank statistic will be used to test the equality of the survival function estimates in the two groups. Cox's Proportional Hazards models will be used to test the effect of the intervention on the time until endpoint events adjusted for age, RCRI, nadir Hb, site, and the interaction terms as described in the primary and secondary endpoint analyses. The analyses will be done on the ITT, mITT, No-Recent-Tansfusion, Completers, and Per Protocol populations.

TABLE 4: Statistical Analysis Schema

Analyses	Statistical Methods	SAS Procedures
Primary Endpoint Composite endpoint at 90 days (Including all cause post-randomization mortality, MI, coronary revascularization, stroke, and acute renal failure)	1. Pearson chi-square 2. Logistic regression adjusted for Age, RCRI, Nadir Hb, Site, and the Interaction terms	1. PROC FREQ 2. PROC GENMOD
Secondary Endpoints 1. Composite endpoint of infectious complications at 90 days (wound infections, pneumonia, sepsis) 2. Composite endpoint of cardiac complications at 90 Days (arrhythmia, CHF exacerbation, cardiac arrest) 3. All-cause mortality after one year 4. Composite endpoint at 30 days (Including all cause post-randomization mortality, MI, coronary revascularization, stroke, and acute renal failure) 5. Length of hospital stay	For Binary Endpoints: 1. Pearson chi-square tests 2. Logistic regression adjusted for Age, RCRI, Nadir Hb, Site, and the Interaction terms For Length of Hospital Stay: 1. Wilcoxon test 2. Quantile regression adjusted for Age, RCRI, Nadir Hb, Site, and the Interaction terms	1. PROC FREQ 2. PROC GENMOD 1. PROC NPAR1WAY 2. PROC QUANTREG
Tertiary Endpoints 1. All cause post-randomization mortality at 90 days 2. Post-randomization MI at 90 days 3. Post-randomization coronary revascularization at 90 days 4. Post-randomization stroke at 90 days 5. Post-randomization acute renal failure at 90 days	For All Tertiary Endpoints: 1. Pearson chi-square tests 2. Logistic regression adjusted for Age, RCRI, Nadir Hb, Site, and the Interaction terms	1. PROC FREQ 2. PROC GENMOD
Other Analyses 1. Baseline characteristics 2. Disposition status 3. Adherence 4. Age of Blood in relation to 90 day composite endpoint, wound Infection, and pneumonia 5. Time-to-event analyses for primary and secondary endpoints	1. Student t or Wilcoxon test, Pearson chi-square or Fisher test, 2. Pearson chi-square test 3. Pearson chi-square test 4. Pearson chi-square tests and Logistic regression 5. Log-rank test and Cox regression	1. PROC TTEST, PROC FREQ, PROC NP1WAY 2. PROC FREQ 3. PROC FREQ 4. PROC FREQ, PROC GENMOD 5. PROC LIFETEST, PROC PHREG

F. Criteria for Study Termination

There will be three interim analysis of the primary oucome measure performed in the studywhen 25%, 50%, 75% of the planned participants completed their participation in the study . If analysis of the primary outcome rates at the time of interim analysis indicates that the null hypothesis can be rejected the study will be recommended for termination for safety reasons.

G. Handling of Missing Data

Every effort will be made to minimize the occurrence of missing data, particularly for the primary and main secondary outcome measures. For the primary outcome, every effort will be made to contact the participants over the phone until participant termination. In the event of a potential drop out, every effort will be made to capture the primary outcome data from the VA databases. For participants who drop out during the study, multiple imputation (MI) method may be used for certain endpoint analyses. Multiple imputations will be based on Rubin's procedure using SAS PROC MI and PROC MIANALYZE. Sensitivity analysis will be performed to compare the results from the imputed data and the complete data without imputation.

H. Reporting of Any Deviations from the Original Statistical Plan

A more detailed statistical analysis plan (SAP) will be generated which will include the details of each statistical analysis plan for each outcome measure along with the suggested table shells for any reports that will be produced during the study and at the end of the study. Any deviations in the statistical plan from the protocol will be specified in the SAP. Any deviations from the SAP will be specified in a revised main manuscript which will be prepared and published at the end of the study.

XVII. STUDY ORGANIZATION AND ADMINISTRATION

A. Requirements for Participating Medical Centers

All participating medical centers must be willing and able to adhere to the study protocol. Minimum requirements for participating medical centers will include:

1. Local Site Investigator. The local site investigator will be an individual with a clinical degree (e.g. psychologist, psychiatrist, nurse) who agrees to support the study enthusiastically and devote sufficient time and energy to ensure that recruitment goals are achieved and that study participants are followed appropriately. The Site Investigator will have at least a 5/8 VA appointment.
2. Study Coordinator. The Site Investigator will recruit a Study Coordinator to assist in all aspects of study conduct including recruitment, participant monitoring, and assistance with all study procedures. The Site Investigator will make all efforts to ensure that the chosen Study Coordinator is competent and enthusiastic. Experience in the conduct of clinical investigation is highly desirable. The Study Coordinator is expected to work diligently with the Site Investigator to meet the goals of the study. In addition, the Study Coordinator will be expected to work collaboratively with the staff at the Chairman's office and the CSPCC.
3. Administrative Support. Each site must provide a letter from the Director and/or the Chief of Staff ensuring that its Site Investigator will receive full administrative support during the conduct of this study.
4. Local Approvals and Reporting Requirements. Sites will be required to agree to allow the VA Central IRB to be the primary IRB for the study and agree to use the VA Central IRB's informed consent template updated only for site specific items in the template (e.g., names of the Site Investigator). Site Investigators will be responsible for coordinating the medical center's interactions with the VA Central IRB. All sites will require Research and Development Committee approval of the study, and some sites may still require local IRB approval. The Site Investigator will be responsible for obtaining initial approval for the protocol and the informed consent form from his/her VA medical center's Research and Development Committee and from the Human Studies Subcommittee/IRB. Copies of the minutes for the meeting documenting approval by these committees or a letter from the Chair of the appropriate Committee stating when the Committee met, what their concerns were, and their final recommendation, will be submitted to the CSPCC before any participants are enrolled at the local center. It will be the responsibility of the Site Investigator to maintain continuing approval of the protocol

at the local site. Documentation of this continuing approval will be submitted to the CSPCC.

5. Global Monitoring and Reporting Responsibilities Delegated. By agreeing to participate in the study, centers delegate responsibility for global monitoring of the ongoing study to the VA Central IRB, DMC, HRC, CSSEC, CSPCC, and the CSPCRPCC. In addition, the local Research and Development Committee and the local Human Studies Subcommittee/IRB will require the Site Investigator to submit annual reports concerning the status of the study for local monitoring purposes.

B. Study Management

CSPCC: The Perry Point Cooperative Studies Program Coordinating Center (CSPCC), located in Perry Point, Maryland, will provide administrative, data processing, and statistical support for the study. All data forms will be submitted to the CSPCC for processing. The CSPCC will edit the data and create the study database. The CSPCC staff will provide guidance on completion of forms, including SAE reports. All reports during the ongoing phase of the study and the final statistical analyses will be the responsibility of the CSPCC. The CSPCC staff will also monitor study progress to ensure that the study is proceeding as scheduled. This team will be headed by the study biostatistician and will include a CSPCC project manager, a statistical programmer, a database programmer, two computer assistants, and a quality assurance nurse.

Office of the Chairman: Chairs will be in routine contact with the participating centers to ensure that the study is performed in accordance with the protocol and to encourage the local study team to keep recruitment and follow-up activities on schedule. The Study Chairman will preside over all meetings of study participants and will represent the study, along with the study biostatistician, at all meetings of outside review committees. The Chairman's Office will be funded with a full-time National Study Coordinator (1.0 FTE).

National Study Coordinator: The National Study Coordinator is responsible for maintaining enthusiasm for the study at all sites, discussing problems of mutual interest related to the study, and identifying any procedural/definitional modifications that might be required. The National Study Coordinator will be responsible to oversee all study activities in the Chairman's Office on a day-to-day operational basis. Specifically, the National Study Coordinator will:

1. Assist the Study Chairpersons in coordinating and administering all aspects of the study;
2. Assist the Study Chairpersons in monitoring the progress of the study;
3. Maintain close contact with the participating investigators/local study research Site Coordinators and assist them in any procedural details of the study:
4. Maintain close contact with the study's supervisory committees; and
5. Work collaboratively with the Perry Point CSP Coordinating Center team to organize and plan periodic meetings of participating investigators for the purposes of reporting progress of the study.

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC): is responsible for monitoring and reporting the safety of trial participants through the review, assessment, and

communication of serious adverse events and serious adverse events reported by study personnel. The CSPCRPCC's responsibilities occur through ongoing communication with the Study Chairman, Executive Committee, Perry Point CSPCC, and CSP Central Office. The reporting activities include the filing of regulatory documents involving adverse events to meet applicable federal regulations and CSP policies. In conjunction with the Perry Point CSPCC, the CSPCRPCC prepares reports safety data for various committees including the Data Monitoring Committee, the IRB, Executive Committee, and the study group. If any new harzards occurs, the CSPCRPCC will prepare and send an approved document to notify all site investigators within after the conference call of the identification of the new safety information.

Endpoint Committee: The Endpoint Committee is a group of experts comprised of a cardiologist, a surgeon, a nephrologist, and an internal medicine/cardiology physician. The committee is responsible for the endpoint outcome measure adjudication.

Study Sites: The Site Investigator at each of the participating medical centers will be responsible for all aspects of the study at his/her site. This includes participant recruitment and follow-up, obtaining initial and yearly local R&D Committee and IRB approvals, ensuring adequate coverage for the study in his/her absence or the absence of other study participating staff, and ensuring the integrity of the study protocol and data from his/her site. A Study Coordinator will be funded for each site and the Site Investigator will be responsible for hiring and supervising this person. In no case should any local Study Coordinator be assigned duties not related to this study. The primary goal for this position is successful recruitment, explaining informed consent, gathering data, and coordination of follow-up assessments. Funding for this position may be terminated or reduced if insufficient participants are recruited and/or data collection and follow-up are deemed to be unsatisfactory. Each Study Coordinator will work with the National Study Coordinator (located at the Study Chairman's office) to develop and to implement a recruitment plan. The Study Coordinator at the sites will participate in periodic conference calls with the other Study Coordinators and study staff.

C. Monitoring of the Study

1. Monitoring bodies

The groups charged with monitoring the various aspects of the study will be the Executive Committee, the Data Monitoring Committee (DMC), the VA's Central IRB, and the Perry Point Human Rights Committee. These committees will meet at regular intervals according to the current Cooperative Studies Program guidelines: prior to the beginning of participant intake and at least every twelve months thereafter. In addition, the CSP Site Monitoring, Auditing and Resource Team (SMART), located at the CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC), will monitor the trial for GCP compliance.

The Executive Committee is chaired by the Principal Proponent and consists of the study Biostatisticians, study Project Manager, study Research Pharmacist, selected participating investigators, and expert consultants. The Executive Committee is concerned with overall study management and is the decision-making body for the operational aspects of the study. The Executive Committee monitors the performance of participating medical centers and quality of

data collected, plans the publications, and oversees the publication and presentation of all data from the study. The Executive Committee must grant permission before any study data may be used for presentation or publication. This committee meets by conference call typically on a monthly basis to review the study progress and meets every 12 months to review blinded study data, decide upon changes in the study, determine the fate of sites whose performance is substandard, initiate any sub-protocols, and discuss publication of the study results.

The Data Monitoring Committee (DMC) will review the progress of the study and will monitor participant intake, outcomes, adverse events, and other issues related to participant safety. The DMC makes recommendations to the Director of the Clinical Science Research and Development (CSRD) Service about whether the study should continue or be stopped. The DMC will include experts in clinical trials, biostatistics, and ethics. These experts will not be participants in the trial and will not have participated in the planning of the protocol. The DMC will consider safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or the unfeasibility of addressing the study hypothesis (e.g., poor participant intake, poor adherence to the protocol).

At each of its meetings during the study period, the DMC will review the randomization rates and assess the difference between the actual and the projected rates, as well as the impact of these assessments on overall trial size. If the study recruitment is inadequate, the reasons for exclusion may be scrutinized and actions may be suggested. An assessment of whether the trial should be continued will be made followed by recommendations, as appropriate. All serious adverse events will be reported on a regular basis to the DMC for their review. Unexpected serious adverse events will be reported to the DMC as soon as they become known based upon the consensus of the Study Chair, the Study Biostatistician, the Director, Perry Point CSPCC, and the Study Pharmacist. The Study Biostatistician will provide the appropriate data to the DMC at specified intervals for this purpose. Conditional power estimates will be provided to the DMC to assist them in making their decisions and recommendations.

As an independent oversight committee, DMC will be monitoring study progress at predetermined time points over the entire duration of the study. The committee will receive analyses of the study recruitment status, demographics of recruited participants, adverse effects, and study protocol adherence on a routine basis. In general, this committee will meet at six to nine months after the start of subject recruitment and yearly thereafter. The committee will receive reports about three weeks prior to their annual meetings and at six-month intervals in between the annual meetings. In order for the DMC to make its recommendation for continuation of the study, it will be necessary for them to see the analyses for the primary outcome measure annually. Periodic monitoring of interim results can significantly affect the probability of making an incorrect decision. A number of formal techniques have been developed for interpreting interim results and the DMC will review these options at their first meeting and prior to the start of data collection. For this study, a Haybittle-Peto interim analysis is proposed. The detailed analysis is described in the biostatistical research and data processing procedure/statistical analysis plan.

The VA's Central IRB will be the study's primary IRB and the IRB of record for the study. It will be responsible for the initial and continuing IRB reviews of the study. The VA Central IRB

must review and approve amendments (changes to inclusion/exclusion criteria, protocols, informed consents, etc), deviations, and review reports about adverse events and problems, complaints, terminations, etc. and that the investigation must provide the VA Central IRB all supporting documentation. The CSPCC will be responsible for providing the VA Central IRB with all materials that are required for each review and to respond to the VA Central IRB's queries and requests for additional materials. The VA Central IRB approves the original informed consent template and any requested changes to the informed consent forms.

The Human Rights Committee (HRC) at the Coordinating Center may be asked to convene if there is any serious adverse event requiring its attention.

Site Monitoring Auditing & Resource Team (SMART) will conduct an initial site visit at each site soon after study start-up. Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART. Monitoring of sites participating in the trial will be executed according to Cooperative Studies Program (CSP) guidelines. Independent routine audits will be conducted at one or more sites per year as determined by SMART. For-cause audits will be conducted as requested by study leadership or the VA CSP Central Office. These audits may be scheduled or unannounced.

The Study Group, which consists of all participating investigators and study coordinators, will meet annually to discuss the progress of the study and any problems encountered during the conduct of the trial.

D. Monitoring data quality and protocol adherence

By utilizing Risk Based Monitoring (RBM), CSPCC will remotely monitor the study team. Each participating site's performances and data quality, completeness of follow-up and adherence to the protocol will continuously be measured. Regularly scheduled conference calls (at least monthly) with the sites, CSPCC and Chairman's office will be held to address data collection, protocol procedures and other issues. Strict adherence to the protocol will be expected of every participating center and will be monitored by the DMC, the Executive Committee, and the CSPCC. Documentation of protocol breaches will be required and any medical center with repeated protocol violations will be recommended to the Executive Committee for termination. If a participating site investigator feels that adherence to the protocol will in any way be detrimental to a particular participants's health or well-being, the interest of the participant must take precedence. In addition, CSPCC, the Executive Committee and the DMC will monitor protocol adherence centrally. The Executive Committee will consider recommending a for-cause GCP audit be conducted by SMART for any site with repeated protocol violations and will consider terminating the site from the trial.
Data quality and the completeness of data retrieval will be closely monitored on an ongoing basis by the Coordinating Center. The study biostatisticians will present interim monitoring reports to the Executive Committee and the DMC that will include the following types of information:

- Participant intake
- Randomization errors
- Breaches of protocol
- Adherence and compliance with original treatment assignment

- Missed study visits
- Completeness of follow-up
- Data quality: data query and error rates
- Audit and site visit results.

If a site is identified as an outlier in terms of data quality, a site conference call or site visit will be initiated to assess the reasons why problems are occurring and how they can be corrected. If the problems continue, the site may be placed on probation or terminated from the study.

E. Monitoring of safety, efficacy and futility

Trial safety will be monitored by CSPCC and the CSPCRPCC, and the Study Chair's Office throughout the study. Safety reports will be submitted to the DMC approximately every 6 months after recruitment begins, or more frequently, if requested by the DMC. For reports to the DMC closed session, serious adverse events will be summarized by treatment groups, and relatedness to the assigned interventions.

The DMC will review the accumulating data and be responsible for determining whether or not to recommend that the trial be stopped for efficacy, futility or safety. Data summaries will be prepared for the DMC for these purposes. Frequent summaries of serious adverse events will be prepared for the DMC for the monitoring of safety, i.e., at least semi-annually. To aid the DMC in their deliberations, other relevant information inside (e.g., secondary analyses) and outside (e.g., other studies) will be made available. Complete details of the interim monitoring plans for the study are given in Section XI: Biostatistical Considerations**.**

XVIII. PUBLICATIONS

A. Publication of Research Results

It is the policy of the Cooperative Studies Program not to reveal outcome data to participating investigators until the data collection phase of the study is complete. This policy is meant to prevent possible biases that might affect data collection. Members of the DMC and the CSPCC Human Rights Committee will be reviewing outcome results to ensure that the study will be terminated early if a treatment is identified as prohibitively dangerous or if a definitive answer is reached prior to the scheduled study termination date.

All presentations and publications resulting from this study will follow CSP policy as specified by the CSP guidelines. The presentation or publication of any or all data collected by participating investigators on participants entered into a Department of Veterans Affairs Cooperative Study is under the direct control of the study's Executive Committee. No individual participating investigator has the right to use this study's data to perform analyses or interpretations, or to make public presentations or seek publication of any or all of the data without the specific approval of the Executive Committee.

The Executive Committee has the authority to establish any number of publication committees, which usually will comprise subgroups of participating investigators and some members of the

Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publication related to this study should be circulated to participating investigators for review, comments and suggestions at least four weeks prior to submission of the manuscript to the presenting or publishing body.

All publications must give proper recognition to the funding source and should list all study personnel(not necessarily as authors of the manuscript). If an investigator's major salary support and/or commitment is from the VA, it is obligatory that the investigator lists the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the usual VA policy; ideally, a subtitle states, "A Department of Veterans Affairs Cooperative Study." The CSP also requires that every manuscript be reviewed and approved by the CSPCC Director prior to submission as a final quality control step. Mechanisms for appeal by a dissatisfied investigator will follow procedures defined by the VA Office of Research and Development.

Participation in Department of Veterans Affairs Cooperative Studies is voluntary. Any investigator who cannot accept these operation guidelines regarding publication policy should not volunteer to participate in the study.

B. Planned Publications

Upon completion of the study, manuscripts will be prepared that focuses on the following objectives:

- Primary publication: Upon completion of the study, a manuscript will be prepared that focuses on the primary outcome, i.e. liberal vs. restrictive composite rates of 90 day all-cause mortality, MI, acute renal failure, coronary revascularization or stroke.
- Other publications: TBD

XIX. REFERENCES

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