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Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)

Jeffrey L. Carson, MD

Study Chairman

Principal Investigator, Clinical Coordinating Center

UMDNJ-Robert Wood Johnson Medical School

New Brunswick, New Jersey

Michael L. Terrin, MD, MPH

Principal Investigator, Data Coordinating Center

Department of Epidemiology and Preventive Medicine

University of Maryland School of Medicine

Baltimore, Maryland

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CHAPTER 1

BACKGROUND AND SIGNIFICANCE

Red blood cell transfusions are extremely common and expensive medical interventions. In the United States, more than 13 million red blood cell units are collected annually and 11 million units are transfused to 3.4 million patients (1). Between 60% and 70% of all red blood cell units are transfused in the surgical setting. The majority of blood transfusions are given to older patients. Despite the common use of red blood cell transfusions in surgical patients, the indications for transfusion in the peri-operative setting have not been adequately evaluated and remain controversial.

1.1 SAFETY OF ALLOGENEIC BLOOD TRANSFUSION

The known risks from blood transfusion are very low. The current risk of transmission of hepatitis C and HIV are about 1:2,000,000 unit (2). Among the more common adverse effects are allergic reaction; febrile, nonhemolytic transfusion reactions; red cell alloimmunization; and leukocyte/platelet alloimmunization. In most patients these events have minimal clinical consequence. Less common, but more serious effects include acute hemolytic reactions, symptomatic hemolytic reactions, and anaphylactic reactions. An additional hazard associated with transfusion in patients with severe chronic anemia is the possibility of circulatory overload with congestive heart failure and pulmonary edema. Human error is also responsible for some adverse effects (3). There is also some evidence that allogeneic transfusion may have an immunomodulating effect that increases the risk of bacterial infections. This risk remains uncertain and it is not known if leukodepletion will reduce the immunomodulating effect of allogeneic transfusion.

1.2 RISKS ASSOCIATED WITH ANEMIA AND CARDIOVASCULAR DISEASE

Red cell transfusions in the peri-operative setting are given to prevent the adverse outcomes associated with anemia. However, the level of anemia that places a patient at significant increased risk of postoperative adverse events is not well understood. Studies in animals suggest a decreased ability to tolerate anemia in the presence of cardiac disease (4-6). Studies in patients who decline blood transfusion for religious reasons performed by the principal investigator confirmed the animal data. In patients with underlying cardiovascular disease the adjusted odds ratio for postoperative mortality began to rise sharply at Hgb level equal to 10 g/dL or less while in patients without underlying cardiovascular disease there was a more subtle rate of increasing risk below 10 g/dL (7).

1.3 ANEMIA AND FUNCTION

Fatigue, weakness, and diminished physical performance are widely accepted clinical signs of anemia. There is strong, but indirect evidence linking hemoglobin levels to function. Treadmill testing in otherwise normal individuals subject to acute anemia by phlebotomy has shown maximal oxygen consumption (VO2 max) to be reduced proportional to the decrease in Hgb level (8;9). Exercise capacity was significantly correlated with the degree of anemia and increased fatigue and decreased energy levels (10). Studies in patients with renal failure treated with recombinant human erythropoietin (EPO) reported improvement in aerobic exercise capacity with increased Hgb level (11-13). Cancer patients treated with EPO experienced increased levels of energy and function (14;15). These data from patients treated with EPO suggest that increasing the Hgb levels in significantly anemic patients (hemoglobin less than 10 g/dL) may increase exercise tolerance and ability to participate in postoperative rehabilitation.

1.4 EFFICACY OF TRANSFUSION IN THE PERI-OPERATIVE SETTING

1.4.1 Observational Studies

The results of the observational studies examining the effect of transfusion on mortality and morbidity vary. The largest studies found higher transfusion thresholds to increase mortality (16;17), reduce mortality (18) and have no effect on mortality (19). The latter study was performed in hip fracture patients. A study in patients with acute myocardial infarction found that transfusion reduced mortality in patients with hemoglobin levels less than 11 g/dL (20). Several small observational studies found improved outcome in surgical patients with cardiovascular disease (21;22). The main limitation of these observational studies is that there may be confounding by indication for transfusion.

1.4.2 Clinical Trials

There are 10 randomized clinical trials that contrasted the effects of different transfusion thresholds (23-32). The clinical settings varied, although each trial randomized patients to be transfused on the basis of a 'conservative' or more 'liberal' strategy. There is overlap between the 'liberal' and 'conservative' transfusion criteria in these trials.

The Transfusion Requirement in Critical Care (TRICC) trial (pilot and main trial) is the only adequately powered study to evaluate clinically important outcomes (27;30). In the main study, the investigators randomized 838 volume resuscitated intensive care unit patients to a restrictive strategy in which patients received allogeneic red blood cell transfusions at hemoglobin levels of 7 g/dL (and were maintained between 7 to 9 g/dL) or to a liberal strategy of receiving red blood cells at 10 g/dL (and were maintained between 10 and 12 g/dL). Average hemoglobin levels (8.5 vs 10.7 g/dL) and red blood cell units transfused (2.6 vs. 5.6) were

significantly lower in the restrictive as compared to the liberal group. The 30-day mortality was slightly lower in the restrictive transfusion group (18.7% vs 23.3%) although the finding was not statistically significant ($p = 0.11$).

A meta-analysis has been performed combining data from five or more trials for six outcomes: probability of red cell transfusion, volume of red cells transfused, hematocrit levels, cardiac events, mortality at 30 days, and overall length of hospital stay (33;34). The pooled data indicated that, on average, a restrictive transfusion trigger reduced the probability of red cell transfusion by 42% (an average saving of 0.93 units of red cells per transfused patient), and resulted in hematocrit levels 5.6% lower on average than in patients who received more liberal transfusions. The effect on length of hospital stay, and the rates of cardiac events were not increased significantly by the use of restrictive transfusion triggers. Restrictive transfusion triggers were also not associated with an increase in mortality, but these results must be interpreted cautiously because the TRICC trial in patients in intensive care unit contributed 83% of the information in the meta analysis of mortality data.

1.5 TRANSFUSION PRACTICE: STANDARD OF CARE

The standard of care related to transfusion practices is difficult to define but most studies suggest that patients are most commonly transfused between hemoglobin concentrations between 8 g/dL to 10 g/dL (hematocrit between 24% and 30%). A 1993 Canadian survey of critical care practitioners and a similar 1998 survey in England found variation in transfusion practice for moderate risk patients. Overall transfusion thresholds ranged from 5.0 g/dL to 12.0 g/dL. However, the mean transfusion thresholds were hemoglobin concentration between 8.0-10.0 g/dL (35; 36). In a study of 78,974 patients with acute myocardial infarction hospitalized between January 1994 and February 1995, transfusion rates varied the greatest in patients with

admission hematocrit between 24% and 30%. Few patients received transfusion above hematocrit of 30% and most patients received transfusion below 24% (37). Two addition studies of critical care patients hospitalized in 1999 report mean pre-transfusion hemoglobin levels of 8.5 g/dL.(38,39) A study of 9,598 hip fracture repair patients hospitalized between 1983 and 1993 (19) demonstrated variability in transfusion practice in the 4,452 patients with a postoperative hemoglobin concentrations between 8 g/dl and 10 g/dl; 2,474 of these patients (55.6%) received transfusions. There was much less variability in transfusion practice below 8 g/dl with 90.5% of patients receiving a transfusion or above 10 g/dl with only 6.6% of patients receiving transfusions.

1.6 SUMMARY OF TRANSFUSION THERAPY EVIDENCE

Except for the pilot study for this trial (29), there are no studies evaluating the safety of withholding blood until patients become symptomatic even though this transfusion strategy is now widely supported by many transfusion medicine experts. There also are no studies evaluating whether symptomatic transfusion is safe in patients with cardiovascular disease. There are no studies that have rigorously evaluated the relationship between anemia, transfusion, and functional recovery. Furthermore, during the past decade blood screening and testing procedures have continually improved and the risk of serious transfusion-associated adverse events is extremely small and difficult to measure. It is therefore critical that we understand whether a more aggressive approach to transfusion is associated with a decreased risk of anemia-associated adverse postoperative outcomes.

CHAPTER 2

STUDY OBJECTIVES

The overall goal of the proposed study is to determine whether a more aggressive transfusion strategy in patients with cardiovascular disease or cardiovascular risk factors undergoing surgery for repair of hip fracture is associated with improved functional recovery and decreased risk of adverse postoperative outcomes.

2.1 PRIMARY AIM:

1. To determine whether a 10 g/dL transfusion strategy is associated with ability to walk 10 feet (or across a room) without human assistance 60 days after surgery compared to a symptomatic transfusion strategy.

2.2 SECONDARY AIMS:

1. To determine whether a 10 g/dL transfusion strategy is associated with unstable angina, myocardial infarction in-hospital or death within 30 days compared to a symptomatic transfusion strategy.
2. To determine whether a 10 g/dL transfusion strategy is associated with myocardial infarction in-hospital or death within 30 days compared to a symptomatic transfusion strategy.
3. To determine if a 10 g/dL transfusion strategy is associated with lower extremity function and instrumental activities of daily living 30 and 60 days after surgery compared to a symptomatic transfusion strategy.

4. To determine if a 10 g/dL transfusion strategy is associated with ability to walk 10 feet (or across a room) without human assistance 30 days after surgery compared to a symptomatic transfusion strategy.

5. To determine if a 10 g/dL transfusion strategy is associated with remaining in a nursing home 60 days after surgery compared to a symptomatic transfusion strategy.

6. To determine if a 10 g/dL transfusion strategy is associated with postoperative, 30-day and long-term mortality compared to a symptomatic transfusion strategy.

7. To determine if a 10 g/dL transfusion strategy is associated with troponin or electrocardiography findings consistent with myocardial infarction compared to a symptomatic transfusion strategy.

2.3 TERTIARY AIMS:

1. To determine if a 10 g/dL transfusion strategy is associated with risk of in-hospital postoperative non-infectious morbidity compared to a symptomatic transfusion strategy. Specific morbid outcomes to be assessed are stroke and thromboembolism.

2. To determine if a 10 g/dL transfusion strategy is associated with risk of in-hospital postoperative pneumonia or wound infection compared to a symptomatic transfusion strategy.

3. To determine if a 10 g/dL transfusion strategy is associated with risk of composite outcome of 30-day mortality, myocardial infarction, pneumonia, stroke or thromboembolism compared to a symptomatic transfusion strategy.

4. To assess the frequency of selected medical errors in a frail, elderly population.

5. To identify patient characteristics that are predictive of successful rehabilitation.

CHAPTER 3

OVERVIEW OF STUDY DESIGN AND METHODS

The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) is a randomized clinical trial designed to test the hypothesis that higher blood transfusion threshold improves functional recovery and reduces morbidity and mortality. Patients who undergo surgery for hip fracture, have a history of cardiovascular disease, and have a postoperative hemoglobin level less than 10 g/dL within 3 days of surgery are eligible. Patients will be randomized to receive enough blood to raise the hemoglobin level above 10 g/dL any time the hemoglobin level is detected to be below 10g/dL during the hospitalization or to receive transfusion if symptoms of anemia develop. Transfusion is permitted but not required if hemoglobin level is less than 8 g/dL. The primary outcome is ability to walk 10 feet (or across a room) without human assistance at 60 days. The most important secondary outcome is postoperative unstable angina, myocardial infarction or death. Medical records will be reviewed while the patient is in the hospital. Patients will be telephoned at 30 and 60 days after entry into the study to determine functional capacity and vital status. Long term mortality will be determined by searching vital statistic registries in US and Canada.

3.1 STUDY POPULATION

3.1.1 Inclusion Criteria

The study population will include patients 50 years of age or older who undergo surgical repair of a hip fracture, with a Hgb levels below 10 g/dL within 3 days following surgery, and who have clinical evidence for cardiovascular disease. Cardiovascular disease will be defined as history of ischemic heart disease or electrocardiogram with evidence for previous myocardial

infarction, history or presence of congestive heart failure or chest radiograph consistent with congestive heart failure, or history or presence of peripheral vascular disease, or history of stroke or transient ischemic attack. Cardiovascular risk factors include history of, or treatment for hypertension; history of, or treatment for diabetes mellitus or fasting blood glucose ≥ 126 mg/dL or random glucose ≥ 200 mg/dL or Hb1Ac above normal range; history of, or treatment for hypercholesterolemia or cholesterol ≥ 200 mg/dL or LDL cholesterol ≥ 130 mg/dL; or current history of cigarette smoking or other tobacco use; or creatinine > 2.0 mg/dL. Hip fracture is defined as fracture involving femoral neck (subcapital, cervical, midcervical, transcervical, intracapsular), intertrochanteric (basilar, basicervical, pertrochanteric or extracapsular), subtrochanteric (proximal femur), or reverse oblique.

3.1.2 Exclusion Criteria

Patients will be excluded from the study if they are unable to walk prior to hip fracture, decline blood transfusions for religious or other reasons, have suffered multiple trauma (defined as a patient who has or has plans to undergo a surgical procedure for traumatic injury to an anatomical site other than the hip), have pathologic fracture of the hip due to malignancy, clinically recognized acute myocardial infarction within thirty days prior to study entry (randomization), have previously participated in the trial and fracture the other hip, have symptoms associated with anemia (e.g., ischemic chest pain) or are actively bleeding at the time of randomization.

3.2 STUDY DESIGN

We will conduct a randomized, unblinded, parallel, two group multicenter trial.

3.3 TRANSFUSION STRATEGIES

Patients will be randomly allocated to the 10 g/dL threshold transfusion or symptomatic strategy. Patients randomly allocated to 10g/dL will receive one unit of packed red cells following randomization and receive enough blood to raise the Hgb level above 10 g/dL any time the Hgb level is detected to be below 10g/dL during the hospitalization. Any transfusion following the initial unit of packed red cells must be preceded by blood test documenting an Hgb level below 10 g/dL.

Patients randomized to the symptomatic transfusion strategy are permitted to receive a transfusion if they develop symptoms of anemia. Transfusion is also permitted in the absence of symptoms if the Hgb level falls below 8 g/dL. Blood is administered one unit at a time and the presence of symptoms is reassessed. Only enough blood is given to relieve symptoms. If the transfusion is given because the Hgb level falls below 8 g/dL, then only enough blood is given to increase the Hgb level above 8 g/dL. All demented patients will be transfused when the Hgb level falls below 8 g/dL because they may not be able to report their symptoms. Symptoms of anemia that will be indications for transfusion in the symptomatic transfusion strategy are as follows: 1) chest pain thought to be cardiac in origin; 2) congestive heart failure; 3) unexplained tachycardia, hypotension, or decreased urine output: signs of volume depletion unresponsive to fluid replacement.

An Hgb level will be measured in all patients days 1, 2, 4, and 7 after randomization. All other Hgb levels are measured as clinically indicated. The assigned transfusion strategy must be followed until discharge or up to 30 days (whichever comes first). Blood must be administered one unit at a time followed by Hgb measurement. A patient in either group may be transfused at

any time without an Hgb level if the patient is rapidly bleeding (e.g., brisk gastrointestinal bleeding) and the physician believes emergency transfusion is needed.

3.4 ENDPOINTS

3.4.1 Primary Outcome

The primary outcome is the patient's ability to walk 10 feet (or across a room) without human assistance at 60 days post-randomization as determined by telephone interview. Patients who are dead at 60 days post-randomization will be classified as unable to walk across a room.

3.4.2 Secondary Outcomes

3.4.2.1 Death, Myocardial Infarction or Unstable Angina

A critical secondary outcome will be post-randomization unstable angina, myocardial infarction in-hospital or death for any reason within 30 days (40). All patients will have electrocardiograms (ECGs) before surgery and prior to randomization, and on post-randomization day 4 and one blood specimen collected for later evaluation of troponin level prior to surgery, one postoperative blood specimen for later evaluation of a troponin level prior to randomization, and on post randomization day 1 and day 4 or prior to discharge (if before day 4). All ECG's performed in-hospital for clinical indications will be collected for use in study outcome evaluations. Troponin samples will be processed, frozen, and stored for batch analyses at the Troponin Core Laboratory. Results of cardiac enzymes performed for clinical indications will be recorded. The ECG Core Laboratory will evaluate electrocardiograms collected in FOCUS using standardized criteria. ECG readings will be combined with interpretations of clinical status and troponin information in the ECG Core Laboratory to assess outcome status for unstable angina and myocardial infarction blind to treatment assignment. We will destroy the

blood sample for the preoperative troponin level for any patient who is not randomized into the study. (see section 7.5)

3.4.2.2 Death or Myocardial Infarction

We will determine the occurrence of the combined outcome post-randomization myocardial infarction in-hospital or death for any reason within 30 days using procedures for assessment of myocardial infarction described in section 3.4.2.1.

3.4.2.3 Other Measures of Functional Status

Lower extremity functioning will be assessed using structured questions from the Functional Status Index. Information about 11 lower extremity tasks will be obtained to determine whether patients used no assistance, equipment or human assistance or if they did not perform the task for health or other reasons during the past week. The eleven lower extremity activities to be included are walking ten feet; walking one block; climbing five stairs; getting into a car; getting in/out of bed; rising from an armless chair; putting on pants; putting socks and shoes on both feet; getting in/out of bath/shower; taking a bath/shower/sponge bath; and, getting on/off the toilet. Higher scores represent greater impairment.

Information on instrumental activities of daily living (IADL) will be obtained using a modified version of the Older Americans Resources and Services Instrument (OARS)(41) which asks about performance of four tasks of daily living during the preceding two weeks. The four activities include: getting to places out of walking distances; shopping for groceries or clothes; preparing meals and doing housecleaning.

We will inquire about fatigue, level of energy and self-efficacy, also.

3.4.2.4 Functional Status at 30 Days

We will telephone patients at 30 days post-randomization to assess ability to walk independently and other functional measures to determine effects of higher blood counts closer to study treatment.

3.4.2.5 Survival

We will measure all cause post-randomization survival. We will determine vital status by telephoning patients after hospital discharge and by searching the National Death Index (for US patients) and Statistics Canada (for Canadian patients) which are updated annually. We will assess mortality up to 60 days post-randomization by telephone follow-up. Long- term survival will be assessed for each patient from the time of randomization to December of year 4 of the study using the National Death Index (for US patients) and Statistics Canada (for Canadian patients).

3.4.2.6 Unstable Angina

Unstable angina will be defined as the new onset of prolonged chest pain ≥ 20 minutes or its equivalent (e.g. dyspnea, hypotension, etc) or ≥ 2 episodes of chest pain of shorter duration believed to be cardiac in origin and for which an ECG was acquired to rule out MI. The ECG Core Laboratory will categorize patients as having unstable angina if (1) the clinical presentation is consistent with the above, (2) the ECG shows interval serial ECG change (e.g. new T-wave inversion, ST depression or elevation) and (3) enzyme criteria do not meet the level required to diagnose MI.

3.4.2.7 Positive Troponin or Electrocardiogram Consistent with Definite Myocardial Infarction

We will assess possible myocardial injury based on the finding of positive troponin or electrocardiogram consistent with definite myocardial infarction.

3.4.2.8 Disposition Status

Disposition status at 60 days post randomization will be classified as follows: nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (e.g., home alone, home with others), retirement home (e.g., sheltered housing, congregate housing, halfway house, or board and care facility), or other. Patients who are dead will be categorized as having an unfavorable disposition, although we will also analyze disposition of survivors. We will document disposition status during the telephone interviews at 30 and 60 days post-randomization described above.

3.4.3 Tertiary Study Outcomes

We will evaluate the morbid events listed below within the hospital stay (up to 30 days post-randomization) time frame. We will only identify morbid events that occur during the hospitalization in which the hip fracture was repaired. We will also analyze each outcome with and without combining it with death. Death is combined with morbidity to avoid the possibility of declaring an advantage for a treatment that is associated with less morbidity but greater mortality.

The outcomes to be evaluated include pneumonia, wound infection, thromboembolism, stroke, composite outcome of death, myocardial infarction, pneumonia, and composite outcome of death, myocardial infarction, pneumonia, thromboembolism and stroke.

We will also be measuring the frequency of selected errors including transfusion errors, use of antibiotic prophylaxis, use of thromboembolic prophylaxis.

3.4.4 Sample Size and Data Analysis

The study will include 2,600 patients. The primary analysis will be performed to test the hypothesis of no difference in ability to walk without human assistance (counting the deceased as unable to walk) between patients randomly assigned to a 10 g/dL Hgb transfusion threshold and patients assigned to a symptomatic transfusion strategy. All analysis will be performed by intention to treat. A Data and Safety Monitoring Board (DSMB) will review the accumulating data for early, convincing evidence of benefit or harm. We anticipate such reports at approximately six-month intervals over the four year duration of patient recruitment and follow-up, so that there will be 7 interim reports and one final report prepared for the DSMB. To take into account the multiplicity of hypotheses being tested in secondary and tertiary analyses, a p-value <0.01 will be required to consider the evidence of differences to be present. The calculations assume 10% cross-over.

The study time line includes 6 months planning and organization. 3.5 years for patient enrollment and data collection, and 1 year for close-out, analysis, and publication.

CHAPTER 4

PATIENT ELIGIBILITY AND PATIENT ORIENTATION

4.1 INCLUSION CRITERIA

1. Patients 50 years of age or older.

2. Undergo surgical repair of a hip fracture.

3. Evidence for cardiovascular disease or cardiovascular disease risk factors. Cardiovascular disease will be defined as history of ischemic heart disease (myocardial infarction, angina pectoris or evidence of coronary artery disease) or electrocardiogram with evidence for previous myocardial infarction, history or presence of congestive heart failure or chest radiograph consistent with congestive heart failure, or history or presence of peripheral vascular disease, or history of stroke or transient ischemic attack. Cardiovascular risk factors include history of, or treatment for hypertension; history of, or treatment for diabetes mellitus or fasting blood glucose ≥ 126 mg/dL or random glucose ≥ 200 mg/dL or Hb1Ac above normal range; history of, or treatment for hypercholesterolemia or cholesterol ≥ 200 mg/dL or LDL cholesterol ≥ 130 mg/dL; or current history of cigarette smoking or other tobacco use; or creatinine > 2.0 mg/dL.

4. Hgb level falls below 10 g/dL in the immediate postoperative period. The immediate postoperative period begins at the time anesthesia is terminated in the operating room and ends at 11:59 PM three days after surgery. The first day after surgery begins at 12:00 midnight the day after surgery was performed. Patients may be randomized even if they received a prior transfusion during the admission

as long as the Hgb level falls below 10 g/dL during the immediate postoperative period.

5. Provide informed consent.

4.2 EXCLUSION CRITERIA

1. Patients who are unable to walk prior to hip fracture.

2. Patients who decline blood transfusions for religious or other reasons.

3. Patients with multiple trauma defined as a patient who has or has plans to undergo a surgical procedure involving traumatic injury to an anatomical site other the hip.

4. Patients who have previously participated in the trial and fracture the other hip.

5. Pathologic hip fracture from cancer.

6. Clinically recognized acute myocardial infarction within 30 days prior to study entry (randomization).

7. Consented patients will NOT be randomized if a) their attending physician is not willing to follow the Protocol (e.g., hemodynamic instability or the patient's physical status); b) the patient has symptoms of anemia (e.g., ischemic chest pain) since this is an indication for immediate transfusion or c) the patient is actively bleeding since this may be an indication for immediate transfusion; d) Clinical Site Director believes the patient is not a suitable candidate for FOCUS (e.g., advanced metastatic cancer).

8. Enrolled in a competing study.

4.3 INFORMED CONSENT

Informed consent will be obtained by properly trained (in human subjects research and FOCUS Protocol) orthopaedic residents, hospital nurses, or Clinical Site Coordinators prior to the patient going to the operating room for surgery. If consent is not obtained prior to surgery, it will be sought postoperatively. If needed, the attending orthopaedic surgeon or the Clinical Site Director could also obtain consent. The patient will be told about the purpose of the study, the two transfusion strategies, that we will review patient charts at the time of discharge, and that the patients will be telephoned at 30 days and at 60 days after surgery. In patients who sign informed consent, a label will be placed on the cover of their charts and a note written in the progress note that identifies the patient as willing to participate in the trial. Patients will always have the option of withdrawing from the study.

Some patients may be too sick or not competent to give permission to enter the study. If the treating physician believes that the cognitive impairment is a reason not to surgically repair the hip fracture, we will not recruit the patient into the study. If the patient will undergo surgical repair of the hip fracture, we will attempt to recruit the patient by seeking permission of a responsible third party. The responsible third party will be identified through inquiry with the patient's physician, hospital administration and, if necessary, family. On making these inquiries, if an individual is identified as holding power of attorney for the patient, informed consent and permission to enroll the patient in the study will be sought from that individual. If there is no individual with power of attorney or medical power of attorney, we will identify and contact the patient's closest, responsible relative ("next of kin"). If there is no responsible next of kin, we will contact the relative or responsible party whose consent allows the hip fracture repair

surgery. If no individual who can be responsible for the enrolling or declining to enroll the patient in FOCUS can be identified, the patient cannot be enrolled.

We believe it is appropriate and ethical to recruit patients who are not competent to give consent into FOCUS because the transfusion policy of choice for these elderly patients is not known, and they are at greater risk of death or one of the morbid events we are assessing than cognitively intact patients. Many of these patients will recover from cognitive impairment with recovery from surgery. Even those who have chronic impairment may enjoy a reasonable quality of life after surgery, and similar patients may benefit from the results of this study. Extrapolation of the results from a study excluding cognitively impaired patients may be unreliable so it is important that direct evidence be obtained by including such patients in the study.

4.4 IDENTIFICATION OF POTENTIAL PATIENTS

At the beginning of the study, each orthopaedic surgeon and anesthesiologist at a Clinical Site will be personally contacted by the Clinical Site Coordinator. Permission will be sought from each orthopaedic surgeon to recruit hip fracture patients. Each site will maintain a list of orthopaedic surgeons not wishing to participate in the trial. Patients of these surgeons will not be approached for recruitment.

The method(s) to identify and recruit patients with a hip fracture after arrival in the emergency room may vary among the Clinical Sites. In Clinical Sites with orthopaedic residents, the residents will explain the study to the patient and obtain informed consent at the time consent is obtained for surgery. The resident will then inform the Clinical Site Coordinator about the patient. To be sure every hip fracture patient is identified, every morning the Clinical Site Coordinator will telephone the admissions office or orthopaedics floor (or other appropriate

place) to identify any hip fracture patients admitted during the prior evening. Since most patients do not go to surgery until sometime later in the day, there is time to recruit the patient. The Clinical Site Director or Coordinator provides positive feedback to the residents by sending a thank you letter which is copied to the Chief of Orthopaedic Surgery. When cases are identified by the Clinical Site Coordinator, the resident is telephoned and any problems are discussed. Each evening prior to the Clinical Site Coordinator going home, the resident on-call is telephoned and reminded about the study and questions are answered.

In Clinical Sites without residents or when the residents are unable to participate, the Clinical Site Coordinator would be responsible for identifying and consenting patients for the study. Assistance may be sought from other hospital personnel. For example, ward clerks or nurses who work on the orthopaedic floors would page the Clinical Site Coordinator when a hip fracture patient is admitted to the hospital. The Clinical Site Coordinator would also make daily telephone calls to the ward or operating room to identify potential patients.

CHAPTER 5

TRANSFUSION STRATEGIES

5.1 10 g/dL THRESHOLD TRANSFUSION

Patients randomly allocated to the 10 g/dL threshold transfusion strategy will receive one unit of packed red cells following randomization and receive enough blood to raise the Hgb level above 10 g/dL any time the Hgb level is detected to be below 10g/dL during the hospitalization. Any transfusion following the initial unit of packed red cells must be preceded by blood test documenting a Hgb level below 10 g/dL.

5.2 SYMPTOMATIC TRANSFUSION

Patients randomized to the symptomatic transfusion strategy are permitted to receive a transfusion if they develop symptoms of anemia. Transfusion is also permitted in the absence of symptoms only if the Hgb level falls below 8 g/dL. Blood is administered one unit at a time and the presence of symptoms is reassessed. Only enough blood is given to relieve symptoms. If the transfusion is given because the Hgb level falls below 8 g/dL, then only enough blood is given to increase the Hgb level above 8 g/dL. All demented patients will be transfused when the Hgb level falls below 8 g/dL because they may not be able to report their symptoms.

Symptoms of anemia that will be indications for transfusion in the symptomatic transfusion strategy are as follows: 1) Chest Pain Thought to Be Cardiac in Origin: retrosternal chest discomfort, chest discomfort described as pressure or heaviness. Myocardial Infarction: chest pain as above, elevated troponin or CPK MB enzymes, new ischemic changes on electrocardiogram. Ischemic cardiac symptoms are associated with a decrease in global and myocardial oxygen delivery; it is prudent to increase the oxygen carrying capacity as one of the

initial treatments. 2) Congestive Heart Failure: dyspnea, orthopnea, or paroxysmal nocturnal dyspnea, S3 gallop, edema without other apparent cause, elevated jugular venous pressure without other apparent cause, new or worsening congestive heart failure on chest radiograph. 3) Unexplained Tachycardia or Hypotension: signs of volume depletion unresponsive to fluid replacement. If these findings do not resolve with adequate fluid resuscitation, then additional oxygen delivery with red cells may be indicated.

5.3 MONITORING HEMOGLOBIN LEVELS

A daily Hgb level will be measured in all patients for the first two days after randomization and on post randomization day 4 (or prior to discharge) and day 7 if the patient remains in the hospital. All other Hgb levels are measured as clinically indicated. The assigned transfusion strategy must be followed until discharge or up to 30 days (whichever comes first).

5.4 TRANSFUSION

Blood must be administered one unit at a time followed by a Hgb measurement. A patient in either group may be transfused at any time without a Hgb level if the patient is rapidly bleeding (e.g., brisk gastrointestinal bleeding) and the physician believes emergency transfusion is needed.

5.4.1 Procedures to Assure Compliance with the Assigned Strategy

Multiple strategies will be employed to enhance compliance with the assigned transfusion strategy. Site and central -based strategies designed to increase compliance will be used.

5.4.1.1 Site-based Strategies

1. Prior to randomization the Clinical Site Coordinator will confirm that the attending physician is comfortable following either transfusion strategy for the eligible patient. If the attending surgeon cannot follow either one of the transfusion strategies for a particular patient, that patient will not be randomized.

2. Following randomization, the patient's chart will be clearly labeled to indicate the assigned transfusion strategy. The Clinical Site Coordinator will contact the attending orthopaedic surgeon, orthopaedic resident (if there is one), and nurse to inform them of the patient's assignment and once again to review the assigned transfusion strategy.

3. The management plan for each strategy requires at least four Hgb measurements on days 1, 2, 4 and 7 following randomization. The Clinical Site Coordinator will monitor the Hgb measurements and verify whether the transfusions were administered or withheld consistent with the assigned transfusion strategy.

4. Clinical Site Director or Coordinator should consider seeking assistance from the blood bank staff to notify study personnel that a blood transfusion has been ordered prior to the release of blood from the blood bank. If administration of blood is a violation of the protocol, study staff should contact the ordering physician to discuss transfusion plans, to clarify the study protocol, and avoid mistakes caused by misunderstandings. This procedure will reduce the chance that a patient is transfused in violation of the protocol. However, study staff do not approve or disapprove the transfusion; care is controlled by the treating physician.

5. Transfusions administered due to symptoms of anemia in patients allocated to the symptomatic transfusion strategy will be carefully monitored; rates will be measured overall and by institution. Clinical Site personnel will be carefully trained with regard to the definition of symptoms of anemia and the need to carefully monitor these types of transfusions. Institutions with higher rates of symptomatic transfusion will be evaluated. In addition, a random sample of the medical charts for patients transfused for symptoms will be reviewed.

6. Patients allocated to the 10 g/dL threshold transfusion strategy will receive one unit of packed red cells following randomization and receive enough blood to raise the Hgb level above 10 g/dL any time the Hgb level is detected to be below 10g/dL during the hospitalization. Any transfusion following the initial unit of packed red cells must be preceded by blood test documenting a Hgb level below 10 g/dL.

5.4.1.2 Central Monitoring for Protocol Violations

Biweekly reports on protocol violations will be prepared by Data Coordinating Center (DCC) and will be included in monthly study performance assessments. Protocol crossovers (failure to properly implement the transfusion protocol) will be followed up during the bi-weekly Management Committee conference calls at which time information provided by the Clinical Coordinating Center (CCC) head nurse in contact with the Clinical Site Coordinator will be reviewed. The Clinical Coordinating Center head nurse will call each Clinical Site bi-weekly to discuss Clinical Site operations, resolutions to problems, and will review bi-weekly performance with the Clinical Site Coordinator.

CHAPTER 6

METHOD OF RANDOMIZATION

6.1 ELIGIBILITY ASSESSMENT

At the time an eligible patient (or family member) provides informed consent the study staff will complete all sections of the pre-randomization forms except for the postoperative Hgb measurements. The Clinical Site Coordinator will be responsible for tracking the postoperative Hgb levels and identifying patients whose Hgb level is below 10 g/dL and therefore eligible for randomization. If a patient's Hgb measurement falls below 10 g/dL during the first three postoperative days the Clinical Site Coordinator must contact the patient's attending surgeon prior to randomization. If the attending surgeon confirms his/her willingness to follow the protocol, the Clinical Site Coordinator will complete the Interactive Touch-Tone Randomization System (ITTRS) form and call the toll-free automated randomization line located at the DCC to obtain the patient's transfusion strategy assignment.

6.2 TREATMENT ALLOCATION RANDOM TREATMENT ALLOCATION PROCEDURES

The DCC staff will prepare randomization schedules for each Clinical Site participating in the FOCUS Trial. The program for generating randomization schedules will have the following characteristics: 1. Treatments are assigned in random order within blocks sizes two, four, six or eight with equal numbers of patients assigned to the symptomatic or 10 g/dL threshold transfusion strategies within each block. 2. Block sizes (two to eight patients per block) are randomly selected with the probability of each block size specified by DCC staff.

The DCC staff will maintain the Interactive Touch-Tone Randomization System (ITTRS) for Clinical Site staff to use to request treatment allocations as eligible patients are identified. The ITTRS system is accessible only to study personnel who enter the password for the Clinical Site and his/her assigned personal identification number (PIN). An individual can request a treatment allocation after he/she has passed training in the use of the ITTRS. Access to the ITTRS is obtained by calling a toll free telephone number at the DCC. The ITTRS prompts authorized users by asking prerecorded questions; users respond by pressing keys on a touch-tone telephone. The prerecorded questions include confirmation that the patient meets all inclusion criteria and has no exclusion criteria and that the patient has given informed consent for enrollment. Depending on the answers to these items, the next available treatment allocation is issued. The treatment allocation is given over the telephone by a prerecorded voice message and confirmed by fax transmission to the Clinical Site. The date and time of the completion of the call is the time of study entry for each patient.

CHAPTER 7

ENDPOINTS

The outcomes in this study were chosen based upon: 1) the importance of the outcome from the perspective of the patient and society, 2) whether a reasonable argument could be made that the outcome could be influenced by transfusion, 3) the ability to cost-effectively assess the outcome, and 4) our ability to accurately assess the outcome in an unbiased manner. Although the outcomes described below are categorized as primary, secondary and tertiary we believe that each one is important and that together they will provide a cohesive package of endpoints to assess the impact of the transfusion strategies. All outcomes will be measured from the time of randomization.

7.1 PRIMARY STUDY OUTCOME – ABILITY TO WALK 10 FEET (OR ACROSS A ROOM) WITHOUT HUMAN ASSISTANCE

The primary outcome is defined as the patient's ability to walk 10 feet (or across a room) without human assistance at 60-days post-randomization. This functional outcome was chosen as the primary outcome because the ability to walk is the primary challenge facing a patient recovering from hip fracture surgery, the ease with which it can be interpreted, and it's strong association with death, nursing home residence, and long-term functional recovery. Patients who are dead at 60 days post-randomization will be classified as unable to walk across a room. Ability to walk will be determined by use of telephone interviews of all patients by asking "In the past 7 days, on average, did you use/receive help to walk 10 feet (or across a room)?" For selected patients, we will also corroborate this study outcome by contacting a proxy. When we are unable to contact a patient, or a patient is unable to provide answers for themselves, we will attempt to interview a proxy for the complete follow-up assessment. We will conduct the

interviews as close to 60 days after surgery as possible but will continue to try to reach the subject up to 90 days after randomization.

7.2 SECONDARY OUTCOMES

7.2.1 Unstable angina, myocardial infarction (in-hospital) or death within 30 days

A critical secondary outcome will be post randomization unstable angina, myocardial infarction or death for any reason within 30 days. All patients will have four cardiac troponin concentrations and three ECG's. Cardiac troponin concentrations will be measured prior to surgery, postoperative prior to randomization, 1 day post randomization and 4 days post randomization or hospital discharge (whichever comes first). The samples will be processed, frozen, and stored for batch analyses. The samples will be shipped to the NHLBI repository every 3 months and sent to the Troponin Core Laboratory every 6 months for analysis. ECGs will be performed prior to surgery, just prior to randomization, and 4 days post randomization or hospital discharge (whichever comes first).

The Myocardial Infarction Classification Committee will adjudicate all suspect acute coronary syndrome events based on the troponin level, electrocardiogram interpretation, and clinical narrative. A narrative (with source documents) will be provided for patients with a history or physical findings consistent with an acute myocardial infarction, ischemia, or ischemic equivalent. All ECGs performed for clinical indications will be interpreted by the ECG Core Laboratory. Results of cardiac biomarkers (troponin or CK-MB) performed for clinical indication will be recorded.

Myocardial infarction in hospital will be classified using The Joint European Society of Cardiology/American College of Cardiology Committee definitions.

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

   a) Ischemic symptoms;

   b) Development of pathologic Q waves on the ECG;

   c) ECG changes indicative of ischemia (ST segment elevation or depression); or

   d) Coronary artery intervention (e.g., coronary angioplasty).

2. Pathologic findings of an acute myocardial infarction.

3. The development of new pathologic postoperative Q waves on the pre-discharge ECG as compared to baseline if biomarkers are incomplete or unavailable.

We will use the criteria for ischemic symptoms from The Joint European Society of Cardiology/American College of Cardiology Committee summary, and the ACC/AHA guidelines for ST segment elevation myocardial infarction and acute coronary syndrome. Possible ischemic symptoms include chest, epigastric, arm, wrist or jaw discomfort with exertion or at rest. The discomfort associated with acute myocardial infarction usually lasts at least 20 minutes, but may be shorter in duration. Symptoms can also include unexplained nausea and vomiting, persistent shortness of breath secondary to left ventricular failure and unexplained weakness, dizziness, lightheadedness or syncope, or a combination of these. These symptoms may be noted in association with chest discomfort or they may occur in the absence of chest symptoms.

Unstable angina is defined as:

1. The absence of elevated cardiac biomarkers as described above.
2. Presence of ischemic symptoms: Angina occurring at rest and prolonged, usually >20 minutes, new-onset angina of at least Canadian Cardiovascular Society (CCS) Class III severity, previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by greater than or equal to 1 CCS class to at least CCS Class III with at least one of the following:
    a) ECG changes indicative of ischemia (ST segment elevation or depression);
    b) Chest pain or angina equivalent leading to a coronary artery intervention (e.g., coronary angioplasty).

7.2.2 Myocardial infarction (in hospital) or death within 30 days

Post randomization myocardial infarction or death for any reason within 30 days will be assessed using the procedures described in section 7.2.1.

7.2.3 Other Measures of Functional Status

Lower extremity functioning will be assessed using structured questions from the Functional Status Index (42). Information about 11 lower extremity tasks will be obtained to determine whether patients used no assistance, equipment or human assistance or if they did not perform the task for health or other reasons during the past week (43). Lower extremity functioning will be measured as a count of the number of activities requiring lower extremity function in which the person is impaired, i.e., requires either human or equipment assistance or both, or is completely unable to perform. The eleven lower extremity activities to be included are walking ten feet; walking one block; climbing five stairs; getting into a car; getting in/out of

bed; rising from an armless chair; putting on pants; putting socks and shoes on both feet; getting in/out of bath/shower; taking a bath/shower/sponge bath; and, getting on/off the toilet.

Information on instrumental activities of daily living (IADL) will be obtained using a modified version of the Older Americans Resources and Services Instrument (OARS) (41) which asks about performance of four tasks of daily living during the preceding two weeks. IADLs will be measured as the count of the number of activities in which the person was impaired, i.e., requires human assistance or is completely unable to perform (43). The four activities include: getting to places out of walking distances; shopping for groceries or clothes; preparing meals; and, doing housecleaning.

Subjective fatigue and self-efficacy within the past week will be assessed. Patients will be queried regarding level of fatigue (using the FACT.An Fatigue scale) and self-efficacy (e.g. feeling able to accomplish tasks).

7.2.4 Functional Status at 30 Days

We will telephone patients at 30 days post-randomization to assess ability to walk independently and other functional measures to determine effects of higher blood counts closer to study treatment.

7.2.5 Survival

We will measure all cause mortality post-randomization. We will determine vital status by telephoning patients after hospital discharge and by searching the National Death Index (for US patients) and Statistics Canada (for Canadian patients) which are updated annually. We will assess mortality up to 60 days post-randomization by telephone follow-up. Long- term survival will be assessed for each patient from the time of randomization to December of year 4 of the

study using the National Death Index (for US patients) and Statistics Canada (for Canadian patients).

7.2.6 Positive Troponin or Electrocardiogram Consistent with Definite Myocardial Infarction

We will compare the frequency of positive troponin or findings of electrocardiogram consistent with definite myocardial infarction between the two treatment groups.

7.2.7 Unstable Angina

We will compare the frequency of unstable angina between the two treatment groups.

7.2.8 Length of Stay in Hospital and Disposition Status

Length of stay in hospital and subsequent disposition status at 60 days post randomization will be assessed. Disposition status classified as follows: nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (e.g., home alone, home with others), retirement home (e.g., sheltered housing, congregate housing, halfway house, or board and care facility), or other. Patients who are dead will be categorized as having an unfavorable disposition, although we will also analyze disposition in survivors. We will assess disposition status during the telephone interview described above.

7.3 TERTIARY STUDY OUTCOMES

We will evaluate the morbid events listed below within the hospital stay (up to 30-day post-randomization) time frame. We will only identify morbid events that occur during the hospitalization in which the hip fracture was repaired. We will also analyze each outcome with and without combining it with death. Death is combined with morbidity to avoid the possibility

of declaring an advantage for a treatment that is associated with less morbidity but greater mortality.

7.3.1 Pneumonia

We will use the Centers for Disease Control and Prevention (CDC) case definition for pneumonia: chest radiograph 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, transtracheal aspirate, bronchial brushings, or biopsy.

7.3.2 Thromboembolism

Thromboembolism will be defined as deep venous thrombosis confirmed by duplex ultrasound, magnetic resonance venography, venogram, or postmortem examination, or pulmonary embolism confirmed by high probability ventilation perfusion scan, pulmonary angiogram, magnetic resonance angiography, spiral CT scan, or postmortem examination.

7.3.3 Stroke

Stroke will be defined as definite if there was evidence of a new hemorrhage or infarction on a magnetic resonance image study, or CT scan of the head, or autopsy and new neurologic deficit lasting $\geq$ 24 hours.

7.3.4 Composite Outcomes

We will evaluate the composite outcome of death, myocardial infarction, and pneumonia and composite outcome of death, myocardial infarction, pneumonia, thromboembolism and stroke since these outcomes are likely to be most closely related to transfusion threshold.

7.3.5 Wound Infection

Wound infection will be defined as a physician diagnosis.

7.3.6 Costs of Treatment

At the completion of the study we will link our data for patients hospitalized within the United States to the Centers for Medicare and Medicaid Services (CMS) Medicare Provider Analysis and Review (MEDPAR). The MEDPAR file contains total charges, covered charges, Medicare reimbursement, and total days for the admission. This will enable us to compare costs between the two transfusion strategies for the Medicare or Medicaid eligible patients in FOCUS.

7.4 MEDICAL ERRORS

Transfusion errors will be defined as ABO incompatible transfusion, and mislabeled specimens. Antibiotic prophylaxis use will be defined as antibiotic given during the day of surgery. Error in thromboembolism prophylaxis will be defined as failure to administer postoperative heparin (> 10,000 units), warfarin, low molecular weight heparin, or fondaparinux.

CHAPTER 8

POST-DISCHARGE FOLLOW-UP

8.1 30 AND 60-DAY FOLLOW-UP STATUS

Trained CCC staff will telephone all study patients twice between 30 and 45 days and between 60 and 90 days after randomization to ascertain vital status, the patient's residence (home, nursing home, etc.), level of fatigue and functional status. The DCC will generate listings of patients due for follow-up which will be sent to the CCC Study Coordinator. The CCC Study Coordinator will generate a report of contact information for the patients using the FOCUS Website data file containing demographic and contact information. This listing will be provided to the CCC personnel responsible for conducting the telephone interviews. Follow-up data will be obtained by the CCC or CCC assigned alternate FOCUS staff. This removes the need for personal identifying information to be maintained at the individual sites or the DCC and helps to protect patient confidentiality.

The window for obtaining follow-up data will be 30 to 45 days and then 60 to 90 days. If the patient or family member cannot be contacted by 90 days after surgery, the patient will be considered lost to follow-up. This interview will take no more than ten minutes once the patient or appropriate proxy is reached. The results of the interview will be recorded on the 30-Day Follow-up Form and 60-Day Follow-up Form. When completed this form will be sent by e-mail to the DCC EMAIL-ENTRY system. No direct, individual identifiers are recorded on any of the forms entered and maintained at the DCC. The original copy of the 30-day and 60-Day Follow-up Form will be filed at the CCC in a cabinet separate from the Demographic and Contact Information Form.

8.2 NATIONAL DEATH INDEX (NDI) AND STATISTICS CANADA

The NDI will be used to assess the long-term mortality status of those U.S. patients discharged alive from the hospital. The NDI is updated in October of each year and includes deaths that occurred during the prior calendar year (e.g. deaths occurring in 2000 were available through the NDI in October 2001.) After October of each year the CCC staff will send NDI a data file that includes patient information required to identify potential matches in the NDI.

The data necessary for linkage to the NDI includes first name, last name, middle initial, Social Security number; month, day, and year of birth, gender and those to assess the quality of the match (state of last known residence, race, marital status). This information will be included in the Demographic and Contact Information FOCUS Website data set. We will submit all patients that have been enrolled in the study. All additional deaths identified through the NDI will be reported by the CCC staff to the DCC staff in an electronic file. We will follow a similar procedure with Canadian patients by obtaining death information from Statistics Canada.

All spin-off data sets submitted to NDI or Canadian death registries will also be backed-up to a zip drive, as will all data received from the registries. A dataset identifying those patients who died and the death date will be generated following the matching of the demographic data with the death registry data. This data set will also be archived on a zip drive, and a copy with only the patient study number, letter code, and date of death will be forwarded to the DCC.

CHAPTER 9

SAMPLE SIZE

9.1 PRIMARY OUTCOMES

9.1.1 Primary Outcome – Ability To Walk 10 Feet (Or Across A Room) Without Human Assistance

The most important measure of functional status proposed for this study is the composite outcome death or inability to walk 10 feet (or across a room) without human assistance at the 60-day follow-up. Based on the pilot study, we anticipate that this outcome will be present in 43% of patients assigned to the symptomatic transfusion strategy. With a test at $\alpha = 0.048$, the study will have approximately power of 0.90 to detect a difference if 36% or fewer of the patients assigned to 10 g/dL threshold transfusion have this outcome (i.e., odds ratio=0.75, relative risk reduction = 16.1%).

9.2 SECONDARY OUTCOMES

To take into account the multiplicity of hypotheses being tested in secondary and tertiary analyses, a p-value <0.01 will be required to consider the evidence of differences to be present.

The analysis of disposition to a nursing home will be performed only in those patients who were not living in a nursing home prior to the hip fracture and assume 5% loss to follow-up as well as 10% cross-over. The study will have statistical power of approximately 0.90 to detect a 20% reduction in risk if 42% of the patients assigned to symptomatic transfusion have this outcome.

The study will have power = 0.90 to detect a relative reduction in 60-day mortality of 41.8%, 1-year mortality of 26.2%, death (30-day), unstable angina or myocardial infarction of

33.8%, death (30-day) or myocardial infarction of 45.1%, myocardial infarction of 71.4%, pneumonia of 45.1%, pulmonary embolism/deep venous thrombosis of 88.2%, stroke of 84.2%, and composite outcome of death at 30 days, pneumonia, myocardial infarction, pulmonary embolism, and stroke of 31.2%. If no medical errors occur in 2600 patients, we will be able to exclude rate greater than 0.12%.

Table 1: Detectable Differences in Other Outcomes

Outcome	Expected Frequency in Symptomatic Transfusion Patients (Reference Group)	Alternative Frequency Detectable in 10 g/dL Threshold Transfusion Patients		Relative Reduction Detectable	
		Power ≥0.80	Power ≥0.90	Power ≥0.80	Power ≥0.90
Death (30-day)	6.6%	3.6%	3.3%	45.5%	50.0%
Death (60-day)	9.8%	6.1%	5.7%	37.8%	41.8%
Death (1-year)	23.7%	18.2%	17.5%	23.2%	26.2%
Death (30-day), unstable angina, or myocardial infarction	14.8%	10.3%	9.8%	30.4%	33.8%
Death (30-day) or Myocardial infarction	8.2%	4.9%	4.5%	40.2%	45.1%
Pneumonia	8.2%	4.9%	4.5%	40.2%	45.1%
Myocardial infarction	2.8%	1.0%	0.8%	64.3%	71.4%
Unstable angina	8.2%	4.9%	4.5%	40.2%	45.1%
Pulmonary embolism/ deep venous thrombosis	1.7%	0.3%	0.2%	79.4%	88.2%
Stroke	1.9%	0.4%	0.3%	76.3%	84.2%
Death (30-day), myocardial infarction or pneumonia	14.8%	10.3%	9.8%	30.4%	33.8%
Death or in nursing home (60-day)	42.0%	34.5%	33.6%	17.9%	20.0%
Death (30-day), pneumonia, myocardial infarction, pulmonary embolism/DVT or stroke	17.0%	12.2%	11.7%	28.2%	31.2%
	Score Scale (Mean and Standard Deviation)	Absolute Score Difference Detectable		Relative Difference Detectable	
Lower extremity function	0-11 (8.90±2.23)	0.30	0.34	3.4%	3.8%
Instrumental function	0-7 (3.33±1.84)	0.23	0.28	7.5%	8.4%

CHAPTER 10

DATA MANAGEMENT, QUALITY CONTROL AND DATA ANALYSIS

10.1 DATA MANAGEMENT

Data collection will occur in three phases: 1) pre-randomization hospital period, 2) post-randomization hospital period, 3) post-discharge follow-up.

10.1.1 Pre-randomization Hospital Period

10.1.1.1 Patient Registration Form

The pre-randomization period is defined as the time between identification of an eligible patient and either randomization or three days after surgery if the Hgb level does not fall below 10 g/dL. Data collected during the pre-randomization period is used primarily for monitoring recruitment and randomization status. We will maintain a registry of all identified potential participants. This will be accomplished by completing the Screening Log for every hip fracture patient presenting to the Clinical Site including those ineligible for any reason. The form will include information on the patient's age, gender, race, and eligibility status (along with selected exclusion criteria.) The completed form will be e-mailed to the Data Coordinating Center (DCC) EMAIL-ENTRY system and reports will be generated by the DCC to be used by the CCC during conference calls with each Clinical Site.

The Screening Log will provide the information needed for the DCC to track recruitment rates and reasons for non-recruitment (e.g., exclusion criteria vs. patient or physician refusal). In addition, this form will allow us to contrast age, gender, and race between recruited and non-recruited patients and assess the comparability of the two groups.

10.1.1.2 Telephone Randomization System Form

For each consented patient the site coordinator will insure that a daily post-operative Hgb measurement is obtained until the measurement falls below 10 g/dL or for three days after surgery (whichever occurs first). If the Hgb does fall below 10 g/dL, then permission must be sought from the attending surgeon to randomize the patient. If permission is obtained from the surgeon, then the clinical site coordinator will complete the Randomization Worksheet and contact the Interactive Touch-Tone Randomization System (ITTRS) maintained by the DCC to obtain the patient's treatment assignment. The ITTRS will assign the transfusion strategy which the clinical site coordinator will record on the Randomization Worksheet. The DCC will send a fax confirmation of the assignment to the clinical site.

10.1.2 Post-Randomization Hospital Period

Immediately following randomization, study personnel will place a label on the patient's chart indicating the assigned transfusion strategy. In addition to the study identification number assigned, the patient will be assigned an additional three-letter code. Both the study number and letter code will be recorded on all study forms.

10.1.2.1 Demographic and Patient Information Form

Following randomization, the clinical site coordinator will complete the Demographic and Patient Information Form. This form provides the information necessary to search the National Death Index and Canadian death registries. A separate US and Canadian form has been developed. The contact information will be used to obtain 30 and 60-day follow-up data.

Because the Demographic and Patient Information Form includes personal identifiers and contact information, it will be maintained at the Clinical Coordinating Center (CCC) rather than

the DCC. This will help insure that medical information is not linked to personal identifiers. Once completed, the Demographic and Patient Information Form will be entered on the FOCUS website accessible for data recovery only to the CCC Deputy Director and Study Chair. The CCC will routinely generate site-specific listings of forms received and entered. The data set will be archived routinely to protect against catastrophic data loss. To maintain the confidentiality of the information, the data will be entered into a password secured file.

10.1.2.2 Clinical Data Form

At the time of randomization, the site coordinator will also complete the Clinical Data Form using information from the medical record and consultation with the surgeon as needed. We will collect data on a few selected variables. History of chronic lung disease: history of, chest radiograph interpretation, or pulmonary function test consistent with chronic obstructive pulmonary, chronic bronchitis, emphysema, chronic restrictive lung disease or asthma; History of diabetes mellitus; History of dementia or confusion: History of confusion, disorientation, global intellectual impairment, or memory loss; Malnourished/cachectic; Type of hip fracture: classified as femoral neck (subcapital, cervical, midcervical, transcervical, intracapsular), intertrochanteric (basilar, basicervical, pertrochanteric or extracapsular), or subtrochanteric (proximal femur); Surgical procedure (total hip arthroplasty, hemiarthroplasty, bipolar hemiarthroplasty, screws/pins, screw and plate combination, girdlestone); Type of anesthesia: general, spinal or epidural; Thromboembolism prophylaxis: warfarin, low molecular weight heparin, intravenous heparin, low dose heparin (5,000-10,000 units, bid -tid), fondaparinux, pneumatic compression stockings, aspirin; Antibiotic prophylaxis: antibiotic administered on the day of surgery prior to beginning surgery and the number of days drug administered; and Pre-admission residence: nursing home (e.g., skilled nursing facility, intermediate care facility,

extended care facility, nursing home), community dwelling (home alone, home with others), retirement home (e.g., sheltered housing, congregate housing, halfway house, or board and care facility), or other. Beta-blocker use: preoperative and postoperative use of beta-blockers (list of drugs will be provided at time of study).

10.1.2.3 Hemoglobin and Transfusion Record Forms

We will record the number of blood transfusions during the preoperative, intraoperative, and postoperative time periods, last preoperative Hgb level, and estimated operative blood loss. For each unit of blood, we record the expiration date so the age of blood can be calculated and if it was leukoreduced (if this is not universally implemented in the US by the start of the study). Transfusion errors will be defined as blood transfusion to wrong person and mislabeled specimens. We will record wrong person transfusion, whether it was ABO incompatible and whether there was a mislabeled specimen. We will obtain this information from the medical record for wrong person transfusion (compare name on transfusion slip) or ABO incompatibility and from the blood bank for mislabeled specimens.

The Protocol requires that Hgb levels be measured at least daily for two days after randomization and on post randomization day 4 (or prior to discharge) and day 7 if the patient remains in the hospital. In addition, an Hgb measurement is required within 24 hours after any transfusion to determine if post-transfusion Hgb targets have been met. This requirement reflects usual transfusion practice. Information on preoperative and intra-operative transfusions and detailed information on post-randomization Hgb levels and transfusions will be recorded by the Clinical Site Coordinator on the Hemoglobin and Transfusion Record Forms. Information on Hgb levels will be obtained by contacting the hospital laboratory directly or from the chart. Information on transfusions will be obtained from the chart.

10.1.2.4 Hospital Outcome Form

The Hospital Outcome Form will be completed by the Clinical Site Coordinator just after the patient is discharged from the hospital, time of death, or 30 days after randomization (whichever occurs first). This form requests information necessary to identify discharge status and the study's morbidity outcomes as defined earlier in this proposal. This form will be completed based on information obtained from the patient's medical record. Site coordinators will consult with the surgeon regarding information on this form as needed.

10.1.3 Transmitting Forms to DCC

The Clinical Data Form, the Hemoglobin and Transfusion Tracking Form and the Hospital Outcome Form will all be e-mailed to the DCC's EMAIL-ENTRY system. All original forms will be stored by the clinical sites in locked file cabinets.

CHAPTER 11

QUALITY CONTROL

The quality of the proposed trial is dependent upon 1) achieving the projected recruitment and randomization rates, 2) the complete and accurate collection of data, and 3) adherence to the assigned transfusion strategy. The investigators recognize that effective quality control procedures are of particular importance in a multi-center study that uses community-based sites. Therefore, we have developed quality control procedures with significant central oversight and designed a governance structure specifically to support community-based sites.

11.1 TRAINING OF STUDY PERSONNEL

The Clinical Site Directors and Coordinators are certified in procedures of key importance to the study prior to initiation of recruitment. Initial training for certification is at the first of the annual collaborators' meetings. The initial 1 ½ day collaborators' meeting will include a thorough review of recruitment procedures; obtaining informed consent; randomization and use of the ITTRS; protocol adherence; and data collection and reporting procedures including use of the EMAIL-ENTRY system. The Clinical Site Coordinators receive detailed instruction on the diagnosis, classification, and treatment of hip fracture. Training methods include a presentation on the Procedures Manual; question and answer sessions; and hands-on experience using the data collection forms and the ITTRS and EMAIL-ENTRY systems. Participants will be provided with sample charts and asked to complete data entry forms. We will emphasize the importance of carefully, accurately, and legibly completing all study forms in a timely manner. We will explicitly describe the need to double check patient social security number, spelling of name, and telephone number. Recommended procedures include reviewing completed forms for missing information and checking for consistency of identification numbers

between forms. In addition, we will describe the pilot study experience with specific reference to identified problems and solutions, effective mechanisms for maximizing patient identification and recruitment, and means of insuring protocol adherence. We will emphasize the symptoms of anemia that are indications for transfusion.

Certification requires passing an examination on the protocol and demonstrated proficiency in required tasks (e.g., completing study forms, using the ITTRS and EMAIL-ENTRY systems.) The DCC staff will work with CCC staff to prepare specific certification procedures. Recertification occurs in association with site visits and is based on the level of proficiency demonstrated in the on-going performance of study activities (e.g., a form failing edit rate less than 10%), and demonstrated expertise. Associate Clinical Site Coordinators will be trained by the Clinical Site Coordinator and Clinical Site Director using materials developed by the CCC and DCC. Small secondary training sessions will be held at the CCC or DCC for Clinical Site staff in need of assistance to improve performance, who are from Clinical Sites joining the consortium after the training meeting or who are replacing previously trained staff under circumstances that do not permit adequate training at the Clinical Site alone (i.e., abrupt departure of certified staff).

Each Clinical Site will be visited during the first two years for the purpose of assessing quality and providing additional training. The site visit team will include a representative of the DCC and CCC. During these site visits, we will provide additional review of the study protocol and procedures. We will also review any problems identified by the DCC quality monitoring procedures and/or during the site visit and recommend possible remedial actions. In addition, the Clinical Site Coordinators will participate in telephone calls with the CCC Head Nurse every two weeks.

Collaborators' meetings will be held annually for all Clinical Site Directors and Coordinators. These meetings will include a review of study procedures, discussion of any problems and solutions, and an update on the status of the trial. It will also provide a forum for open discussion among the collaborators and generate continued enthusiasm for participation in the trial.

11.2 QUALITY MONITORING

11.2.1 Data Collection

The DCC has primary responsibility for monitoring data collection, providing protocol adherence review, and initial editing of the reported data, with the exception of the Demographic and Patient Information Form which the CCC will edit. All forms entered via the E-MAIL-ENTRY system will be evaluated by a central edit program designed to detect items out-of-range, inconsistent sets of items and combinations of items that are incomplete. Results of the edit will be reported in the DCC Quarterly Report.

The CCC will review all Demographic and Patient Information Forms for completeness and legibility. CCC staff will contact the Clinical Site Coordinator to clarify any important missing or illegible information.

In addition to these standard editing procedures, the medical charts of the first two randomized patients after the start of the study (or at the time the Clinical Site Coordinator changes) from each site and a random sample of 10% of patient medical records will be carefully reviewed by the CCC Head Nurse to insure the accuracy of the data abstraction process. The DCC will generate a listing of the study identification numbers of the patients whose charts will be reviewed. This will be sent to the Clinical Site Coordinator at the Clinical Site who will then

copy the chart and forward to the CCC. The DCC will also forward the listing of identification numbers along with a computer printout of the data items to the CCC. CCC staff will compare the data entered with the data in the medical chart and record whether or not each data point was verified. This review will be designed to identify problems in recording data, data entry, data processing, as well as protocol adherence. The results of the review will be discussed during the telephone calls with the CCC Head Nurse every two weeks and will be forwarded to the DCC staff for inclusion in the Quarterly Report.

A second staff member of the CCC will listen to functional status interviews in a random sample of 25 interviews each year. Findings will be compared and if inaccuracies are found, methods to improve performance will be instituted with the CCC leadership.

11.2.2 Recruitment and Randomization Rates

The DCC will carefully monitor recruitment, minority representation, and randomization rates and reports will be prepared and distributed biweekly to the Management Committee and CCC Head Nurse (to be used during telephone calls with Clinical Site Coordinator) every week and will be sent in monthly reports to each site and the Steering Committee.

If recruitment is low for a site, we will review with the Clinical Site Coordinator and Clinical Site Director how recruitment is organized and implemented. We will use data from Patient Registration Form to identify which stage(s) of recruitment is the problem (number of patients presenting to hospital, exclusion criteria, consent rate, attending surgeon refusal, postoperative Hgb > 10 g/dL, etc). This will aid the CCC nurse in providing custom solutions for the problem. If the CCC or DCC staff are unable to solve the problem, then study leadership will seek assistance from Clinical Site Coordinators with excellent recruitment rates.

It may be helpful for the Study Chairman to present rounds for surgical and/or medical departments. This would provide the opportunity to answer questions and to generate excitement for the trial. If the problem is one of the opinion leaders at the hospital is not supportive of the study, the Study Chairman will offer to telephone this person.

11.2.3 Detection of Protocol Violations

Protocol violations include the failure to obtain the required Hgb measurements during the pre-randomization and post-randomization phase as outlined in the protocol, failure to complete and submit the required forms, and failure to adhere to the assigned transfusion strategy. Both the DCC data editing process and the more thorough review of a subset of charts will be used to identify violations. These will be discussed with the Clinical Site Coordinator during telephone calls with the CCC Head Nurse every two weeks and reported in the DCC Quarterly Performance Report.

11.2.4 Response to Protocol Violations

Major protocol violations are those that undermine the fundamental premise of the study (such as failure to administer the assigned treatment strategy). The initial response to a major protocol violation will be remedial efforts such as conference calls, site visits and development of procedures to prevent the violation from reoccurring. However, if remedial efforts fail to address the problem (e.g., failure to maintain a treatment crossover rate < 10%), ITTRS function for that site will be suspended pending review by the Management Committee, DSMB, and NHLBI. This review could result in either more aggressive remedial efforts or termination of the Clinical Site. Minor violations are those that impede progress of the study such as not submitting data in a timely fashion (form delinquencies). Clinical sites will only receive payment for cases after completed forms are submitted.

CHAPTER 12

DATA ANALYSIS

12.1 INTRODUCTION

The primary analysis will be performed to test the hypothesis of no difference in ability to walk 10 feet (or across a room) without human assistance (counting the deceased as unable to walk) between patients randomly assigned to a 10 g/dL Hgb transfusion threshold and patients assigned to a symptomatic 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 analysis will be performed by intention to treat.

12.2 INTERIM MONITORING

A Data and Safety Monitoring Board (DSMB) will review the accumulating data for early, convincing evidence of benefit or harm. We anticipate such reports at approximately six-month intervals over the four year duration of patient recruitment and follow-up, so that there will be 7 interim reports and one final report prepared for the DSMB. To maintain the overall Type I error rate at $\alpha = 0.05$, while performing interim monitoring for the primary outcome, we propose to use the Fleming-Harrington-O'Brien method. (46) With this approach, more stringent evidence of treatment differences is required at the initial analysis than at later interim analyses, and the final interim analysis is performed at close to the overall α-level for the study. The monitoring bounds for this study are displayed in Table 2.

Table 2: Monitoring bounds for interim analysis

Analysis	p-value needed to reject null hypothesis
1	0.00072
2	0.00079
3	0.00096
4	0.00120
5	0.00124
6	0.00157
7	0.00158
Final	0.04807

12.3 PRIMARY ANALYSIS

A variety of analytic methods will be used for primary, secondary and other analyses (Table 3). The primary study outcome will be survival with ability to walk 10 feet (or across a room) without human assistance 60 days after surgery. This outcome will be compared according to assigned transfusion strategy (analysis by intent to treat), using the Mantel-Haenszel chi-square test, taking into account different Clinical Sites. (47) The test for differences between transfusion strategies in the primary outcome will be conducted at an overall α-level of 0.05.

Prior to performing the primary outcome analysis, the Breslow-Day test for homogeneity of the odds ratio will be used to assess if there is significant (at α=0.05) evidence of differences

in the effect of treatment according to Clinical Sites. (48) The proposed strategy for dealing with treatment x Clinical Site interactions should maintain the overall α-level of the primary outcome analysis at 0.05 since the test for average treatment effect and for interaction effect will be statistically independent. This clinic-treatment interaction is of concern for two reasons: (1) systematic variation such as deviations from Protocol (as opposed to random error) in treatment effect among clinics may reduce the power of the study; and (2) conceivably, a large treatment effect in a few clinics may result in an overall treatment effect in the study because of the particular patient population in those clinics.

If an interaction between treatment and Clinical Site exists, the assumptions of the Mantel-Haenszel chi-square test of overall treatment effect will not be met and an overall estimate of the odds ratio does not make sense. In that case, we will review the Clinical Sites' performance and results to determine the nature of the differences in treatment effects. If there is no interaction, the Mantel-Haenszel chi-square procedure will be used to estimate the overall odds ratio across all Clinical Sites. Secondary analyses will be conducted using logistic models to adjust for other clinical factors, such as age, sex, type of hip fracture, surgical procedure, and type of anesthesia.

12.4 SUBGROUP ANALYSES

Logistic regression will be used in this large, well-described patient population to explore three patient characteristics (age, gender, race/minority status) for differences in treatment effect for dichotomous outcomes, especially the primary outcome -- ability to walk 10 feet (or across a room) without assistance. A typical model for this study might be:

$$p(\text{outcome}) = [1+\exp(-\beta_0-\beta_1 tx-\beta_2 age-\beta_3 gender-\beta_4 race/minority\ status - interaction\ terms)\ ]^{-1}.$$

In the above model, tx stands for transfusion strategy. The tx by age, tx by gender and tx by race/minority status interaction terms in these models will be used to test whether patient characteristics modify the magnitude of the treatment effect. Also, we will test all treatment effects for interaction with status as having cardiovascular disease or not having cardiovascular disease at the time of study entry.

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.(49) 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. (49) 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 a log-linear model.

12.5 OTHER OUTCOMES AND ANALYSES

For secondary analyses, to take account of the multiplicity of hypotheses being considered, a p-value < 0.01 will be required to consider that some evidence of differences are present. Secondary outcomes are analyzed with $\alpha = 0.01$ to adjust for multiple comparisons; a more stringent alpha level reduces the likelihood Type I to some extent. This adjustment does not involve the primary outcome comparison or alpha spending plan.

Secondary outcomes to be considered include mortality the occurrence of myocardial infarction or unstable angina in hospital or death within 30 days of study entry, other measures of functional status at 30 days and 60 days, death or disposition to a nursing home at 30 days and 60

days, and in-hospital, pneumonia, stroke, myocardial infarction, and pulmonary embolism/deep venous thrombosis (Table 3).

With the data we plan to collect on 1300 patients managed according to a 10 g/dL transfusion threshold and 1300 patients managed according to a symptomatic strategy, we will have an opportunity to evaluate prognostic indicators of short-term recovery that have not been adequately considered previously. Among the issues that we will evaluate are: surgical procedure, type of prosthesis used, and anesthesia type. We also will identify characteristics of patients who do better in each treatment group.

Binary outcomes will be considered as present/absent variables, and the effect of treatment on these outcomes will be analyzed initially with a chi-square test. Additional analyses, taking account of other patient characteristics such as age and gender, will be performed using logistic regression. Outcomes in multiple categories (e.g., death, nursing home residence and living in the community) will be analyzed in 2 x k contingency tables using chi-square tests with more than one degree of freedom. Time to death in long-term follow-up will be analyzed with log rank statistics. Functional status scores (lower extremity physical activities of daily living -- PADL -- and instrumental activities of daily living -- IADL) will be analyzed with t-tests. Each scale item is given a value of 0 (requires no help to do) or 1 (requires human or equipment assistance or does not perform for a health reason) before items are added to create a score. If items are not routinely performed for a non-health related reason, it is treated as missing. If $\leq$ 3 PADL items or $\leq$ 2 IADL items are missing, then the summary score is computed by giving the missing item(s) the average of other scale items. If more than 3 PADL or 2 IADL items are missing, the scale score is considered missing for that subject.

Losses-to-follow-up are expected to be few for disposition and functional status based on our pilot experience and the relative lack of mobility of these patients in the first months after surgery. Losses-to-follow-up are not anticipated for vital status with the use of the National Death Index and Canadian Death Registries. Sensitivity analyses will be performed to assess the impact of loss-to-follow-up. These will include assuming that all patients lost to follow-up have good outcomes, (e.g., able to walk 10 feet (or across a room) without human assistance or living in the community), all patients lost to follow-up have bad outcomes (e.g., not able to walk 10 feet (or across a room) without human assistance or living in a nursing home), that patients in the treatments have good or bad outcome in opposite fashion (i.e., one treatment's losses to follow-up always have good outcomes and the other treatment's always bad outcomes), and mixed possibilities.

Observational analyses will be conducted of the associations between patient characteristics and success of rehabilitation (i.e., ability to walk 10 feet (or across a room) without human assistance and functional status scale scores). Logistic regression models will be fitted to test for associations between characteristics and ability to walk 10 feet (or across a room) without human assistance. GEE models will be used for functional status outcomes at 30 days and 60 days.

Observational analyses will be conducted of the associations between characteristics of transfused blood and two outcome measures (death and occurrence of pneumonia). Current data collection plans call for the age of each unit of blood transfused and leukodepletion status to be recorded. 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) or use of non-leukodepleted blood (entered in models as use of

any non-leukodepleted blood, number of units of non-leukodepleted blood transfused or as variables that involve leukodepletion status and method of leukodepletion (if used)). Observational analyses will be adjusted for patient characteristics such as age and gender which are associated with the occurrence of death and pneumonia.

Table 3: Analysis Methods for Performing Primary, Secondary and Other Analyses

1. Primary End Point Analyses	
Ability to walk 10 feet (or across a room) without human assistance comparing two treatment groups by intention-to-treat	Mantel-Haenszel Chi-square, Chi-square test with one degree of freedom, and with more than one degree of freedom, and logistic regression
2. Secondary Analyses	
a) Baseline characteristics in each treatment group	Descriptive statistics (means, standard deviations, percentages)
b) Adherence	Chi-square tests with one degree of freedom
c) Baseline characteristic effects on outcomes (including Predictors of Rehabilitation success)	Multiple logistic regression and Generalized Estimated Equations (GEE)
d) Death or myocardial infarction	Log Rank Tests and Cox Proportional Hazards Regression. Chi-square test with one degree of freedom.
e) Disposition status	Chi-square tests with one degree of freedom, and with more than one degree of freedom
f) Mortality (time to death)	Log Rank Tests and Cox Proportional Hazards Regression. Chi-square test with one degree of freedom.
g) Mortality (post operative - 30-day)	Chi-square test with one degree of freedom.
3. Other Analyses	
a) Morbid outcomes (i.e., pneumonia, wound infection, stroke, myocardial infarction, unstable angina, chest pain, pulmonary embolism in univariate or combinations)	Chi-square tests with one degree of freedom, and with more than one degree of freedom
b) Functional Status scores (*PADL, IADL)*	T-tests
c) Blood Transfusion Characteristics (i.e., leukodepletion status and red cell age) in relation to death and pneumonia	Logistic Regression
d) Medical errors	Point estimates with 95% confidence intervals based on the binomial distribution

CHAPTER 13

STUDY ORGANIZATION

13.1 PARTICIPATING UNITS

The participating units in FOCUS integrate with the FOCUS administrative structure to form the study organization (See Exhibit 13-1)

13.1.1 Clinical Site

At each collaborating hospital, a Clinical Site Director and Clinical Site Coordinator will be identified. These two people will work closely together to assure successful performance of the trial.

13.1.1.1 Clinical Site Director

The responsibilities of the Clinical Site Director include: 1) To insure that all medical staff involved with the care of hip fracture patients are well informed about the trial; 2) To insure that all patients with hip fracture are routinely considered for the trial and that their post-recruitment hemoglobin levels are checked for eligibility for randomization; 3) To insure that the treatment assignment is followed, i.e., blood is given in the symptomatic transfusion group only for symptoms from anemia or when the lower threshold is reached and blood is given in the 10 g/dL transfusion threshold group when Hgb < 10 g/dL; 4) To communicate with Clinical Coordinating Center staff and Data Coordinating Center staff any problems or concerns related to the study; and 5) To assist the Clinical Site Coordinator as necessary.

13.1.1.2 Clinical Site Coordinator

The responsibilities of the Clinical Site Coordinator include: 1) To identify all hip fracture patients for the trial; 2) To obtain informed consent from the patient or family if not

obtained by the orthopaedic surgeon or resident; 3) To enroll the patient in the study by telephoning the randomization service; 4) To inform the surgeons and nurses caring for the patient of the patient's treatment assignment; 5) To complete data collection forms and process data edit queries; 6) To insure compliance with the study Protocol; 7) To e-mail or fax data forms to the Data Coordinating Center and arrange for copying and mailing of medical records to the Clinical Coordinating Center for quality assurance; 8) To insure the emergency room and orthopaedic wards are stocked with trial materials; 9) To participate in telephone calls with the Clinical Coordinating Center head nurse; 10) To train assistant site coordination and other staff at the Clinical Site; and 11) To maintain all Clinical Site study materials.

13.1.2 Clinical Coordinating Center

The Robert Wood Johnson School of Medicine, Division of General Internal Medicine will be responsible for clinical coordination of the trial. The responsibilities of the Clinical Coordinating Center are to: 1) Provide administrative and fiscal support for the Clinical Sites; 2) Provide technical, patient assessment and Protocol adherence advice to Clinical Site staff; 3) Perform telephone follow-up data collection at 30 days and 60 days post-randomization for enrolled patients; 4) Perform National Death Index and Canadian Death Registry searches for deaths of patients enrolled; 5) Assist Clinical Sites to correct problems with recruitment, Protocol adherence and data collection; 6) Participate in site visits; 7) Provide advice about any aspect of the trial; and 8) Lead presentation and publication of study results for the scientific and lay press.

13.1.3 Data Coordinating Center

The Department of Epidemiology and Preventive Medicine, University of Maryland School of Maryland, Baltimore, Maryland, will be responsible for data coordination of the trial. The responsibilities of the Data Coordinating Center are to: 1) Provide all study materials to

centers; 2) Provide a 24 hour randomization service; 3) Receive data collection instruments and to verify them for completeness, retrieving any missing data from the centers; 4) Enter data into a computer database and conduct routine data edits; 5) Monitor performance to detect problems with recruitment, Protocol adherence and data collection; 6) Participate in site visits; 7) Provide advice about any aspect of the trial; 8) Perform interim and final analyses.

13.1.4 Electrocardiographic Core Laboratory

The Electrocardiographic (ECG) Core Laboratory will be responsible for the standardized interpretation of electrocardiograms (ECGs) in FOCUS. Using labels provided by the DCC to obscure patient identification, Clinical Sites will send ECGs, narratives and cardiac enzyme/troponin level results to the ECG Core Laboratory; the ECG Core Laboratory will send electronic files of ECG readings and outcome classifications to the DCC. The DCC will direct a limited number of blinded ECG resubmissions to the ECG Core Laboratory for quality control. ECG Core Laboratory ECG interpretations, clinical course narratives and Clinical Site troponin (and CPK-MB) measurements will be used in the classification of myocardial infarction outcomes.

13.1.5 Troponin Core Laboratory

The Troponin Core Laboratory will be responsible for measurement of troponin T and I concentrations. Specimens will be processed every 6 months and results will be forwarded to the Data Coordinating Center for incorporation into the trial database. The Troponin results will be provided to the ECG Core Laboratory for classification of myocardial infarction outcomes.

13.1.6 Study Chairman

Study Chairman responsibilities will include: 1) To provide overall organization of the trial; 2) To serve as Chair, Steering Committee; 3) To administer the Data Safety Monitoring Board; 4) To work with the Clinical Sites and Data Coordinating Center to maximize collaboration and to arrange study meetings; 5) To provide collaborators with information about the progress of the trial; 6) To participate in visits to the Clinical Sites to assess quality and assist with problems; 7) To take a leadership role in defining the analysis of study data; 8) To prepare the manuscripts describing the design and results of the study. In addition, the Study Chairman's office will be responsible for performing searches of vital statistics registries, telephoning all subjects 60 days after study entry to determine disposition status and functional status.

13.1.7 Clinical Chairmen

The US Clinical Chairman and Canadian Clinical Chairman of the study and each will serve as members of the Steering Committee. Besides contributing to the study design from the perspective of Orthopaedic Surgery, they will assist with initiating and visiting Clinical Sites, and coverage outside of routine office hours on-call to answer Clinical Site staff's questions about the study.

13.2 ADMINISTRATIVE STRUCTURE

13.2.1 Steering Committee

A Steering Committee will be responsible for overseeing the study. This committee will make major organizational and policy decisions. The committee will include Study Chairman, Study Clinical Chairs, representatives of Data Coordinating Center, and other representatives, and two of the Clinical Site Directors, to be selected by the other Clinical Site Directors. The

NHLBI project officer will be invited to participate. This group will have quarterly conference calls and meet yearly prior to the annual Clinical Site Directors and Coordinators meeting.

13.2.2 Management Committee

A smaller committee involved with the day to day running of the study will have conference calls every two weeks to discuss the progress of the trial (including recruitment and protocol violations). This group will be composed of Study Chairman, Clinical Chairs, Chair and Deputy Chair of Data Coordinating Center, and Deputy Chair of Clinical Coordinating Center. The Clinical Coordinating Center head nurse will participate as necessary to report on problems identified on individual Clinical Site bi-weekly contact.

13.2.3 Publications and Ancillary Studies Committee

A Publications and Ancillary Studies Committee will be formed from the study leadership (Data Coordinating Center staff and Clinical Coordinating Center staff) and leading Clinical Site Directors. This committee will review all proposals for and final versions of research abstracts, presentations, and manuscripts to be submitted to journals and national meetings. The committee will also review proposals for ancillary studies. Since the success of the trial depends entirely upon the collaboration of the doctors and nurses in the participating hospitals, credit will be assigned to them (as the “FOCUS Research Group”) in the authorship of reports from the study. Each Clinical Site Director and Clinical Site Coordinator will be named personally in an appendix to the main report.

13.2.4 Data and Safety Monitoring Board

Members of the Data Safety and Monitoring Board (DSMB) will be appointed by and report to the National Heart, Lung, and Blood Institute (NHLBI) director. They will monitor

accruing data in order to confirm that the patients in the trial are being cared for safely. The DSMB will be responsible for:

1. Reviewing and analyzing the progress of the study.
2. Approving amendments to the trial Protocol, if warranted.
3. Monitoring the safety of the study treatments.
4. Reviewing data quality.
5. Reviewing interim analyses and recommending early stopping or continuation of the trial.

The DCC and the Management Committee provide input to this committee as requested. The DSMB will review study data reports including primary end point analysis every six months either in a meeting or on a conference call.

13.2.5 Role of DCC Staff

At least one DCC staff member will be assigned to each study committee and subcommittee to participate in all meetings and conference calls. The DCC Director or Deputy Director will serve as Executive Secretary of the Steering Committee; Management Committee; Publications and Ancillary Studies Committee; and will work with the Chairperson of each committee to draft the agenda, summary notes, and lists of action items for each meeting or conference telephone call.

The Executive Secretary of the Publications and Ancillary Studies Committee will supervise the development and implementation of a system to track preparation and review of study manuscripts and abstracts on main results, databank studies and ancillary studies to disseminate the design, methods and results of this trial.

13.2.6 Data Coordinating Center Interface with Clinical Coordinating Center

Conference calls, facsimile transmission, e-mail and courier will be used to maintain frequent and regular communications between the Clinical Coordinating Center and the Data Coordinating Center. The investigators will discuss study activities in person or by telephone every two weeks during the Management Committee conference calls. The NHLBI Project Officers will be invited to participate in these meetings and calls. These calls serve to review study progress and Protocol adherence at the participating Clinical Sites, review committee activities, and plan study meetings. DCC staff will develop computer programs for use by CCC staff to enter follow-up demographic and telephone contact information in a secure, study specific Microsoft Access database. CCC staff will travel to Baltimore four times per year to meet with Data Coordinating Center staff. In the first months of FOCUS, CCC and DCC staff will develop training sessions for Clinical Site staff, and in the last months they will lead manuscript preparation efforts. Documents and materials for training and draft manuscripts will be reviewed with the Management Committee as will plans for long-term archival of study data.

13.2.7 Data Coordinating Center Role in Training of Study Personnel

Prior to the start of recruitment and in conjunction with the training session planned by the Clinical Coordinating Center, DCC staff will organize training for Clinical Site staff to review enrollment of patients using the Interactive Touch-Tone Randomization System (ITTRS), data collection procedures, submitting forms by e-mail or fax to the DCC, and responding to edit queries. DCC staff will monitor each Clinical Site to assure that staff at each site have completed the required training, and that all other steps necessary to begin participant recruitment are completed. Clinical Site staff who have completed training procedures in

Clinical Sites that are approved to participate in FOCUS will be given certification numbers that will be used to track the individual responsible for each data item and activity in FOCUS.

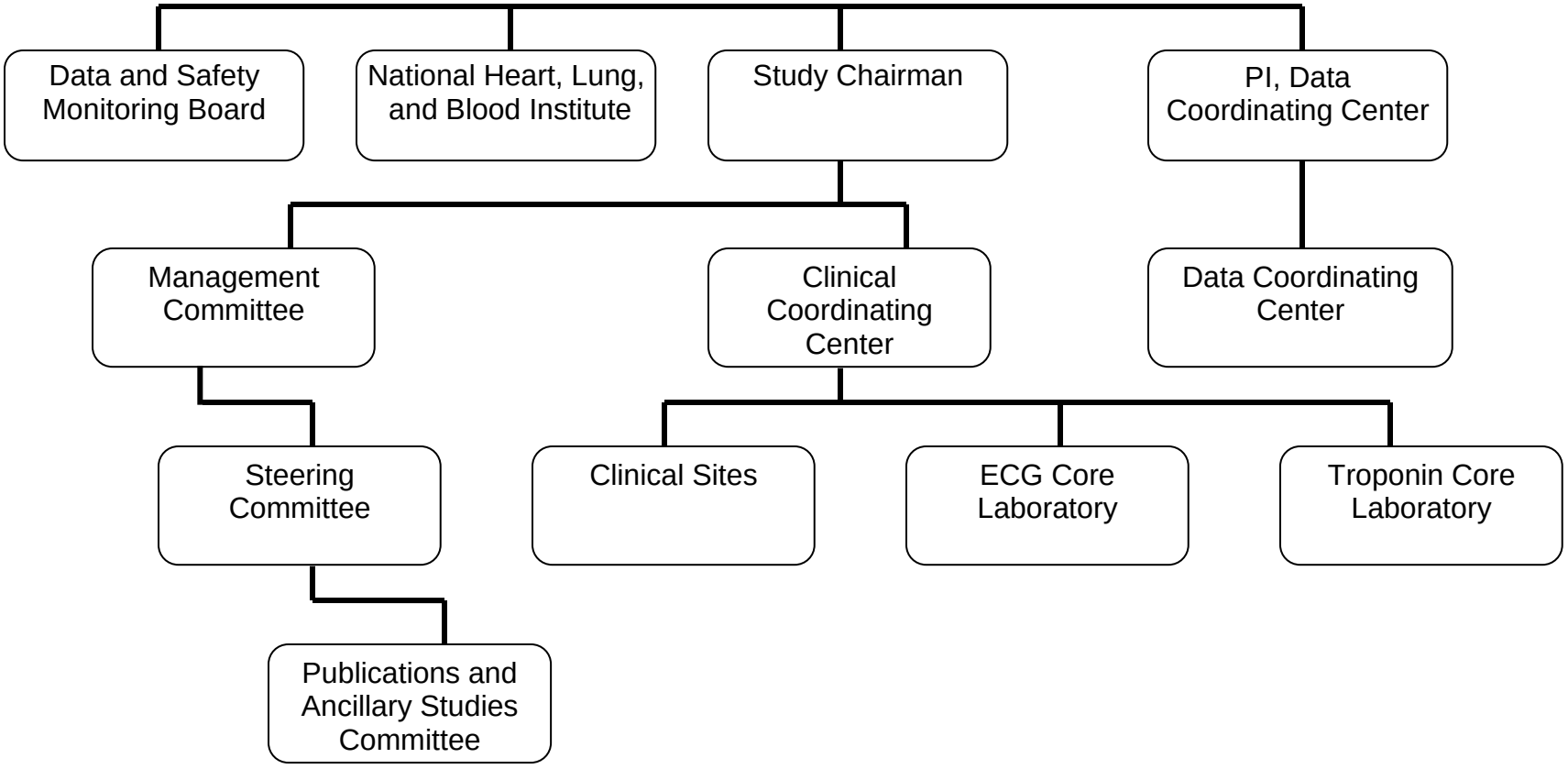
13.3 STUDY TIME LINE

The study will last five years and be broken into the following phases. 1) Planning and Organization Phase 1 (months 1-4): Finalize the Manual of Operations and data collection instruments. Communicate with the Clinical Site Directors at each study sites. Obtain IRB approval at clinical sites with assistance from CCC staff. Develop computer software for randomization and data entry. This time period is feasible because we a) are implementing the protocol that was used in the pilot study, b) the forms we will be using have been extensively tested, and c) we have staff from CCC responsible for completing IRB application. The development of computer software and manual of operations will be addressed quickly at the beginning of the study. 2) Planning and Organization Phase 2 (months 5-6): Communicate final study protocol and procedures. Plan and schedule training. Hire Clinical Site Coordinators. Hold annual Collaborators' Meeting for Clinical Site Directors and Coordinators. Distribute final forms. 3) Recruitment and Follow-up Phase (second half of Year 1, Years 2, 3, and 4): Initiate patient enrollment and continue for 3.5 years or until patient recruitment is completed or the study is stopped early. Hold annual Collaborators' Meetings. Visit Clinical Sites once during the first year of patient recruitment and subsequently on an as-needed basis. CCC prepares and distributes quarterly newsletters. Bi-annual meetings (either in person or via conference call) of the Data and Safety Monitoring Board. 4) Close-out and Analysis Phase (Years 5): Complete follow-up and data cleaning. Perform data analysis. Discuss results at collaborators meeting. The extra half-year is needed to complete the searches of the national vital statistics registries.

Prepare manuscripts and final reports. A one-year, no-cost extension will be requested of the NHLBI if necessary to meet recruitment goals.

Exhibit 13-1

Study Organization Chart



CHAPTER 14

POLICY MATTERS

14.1 PUBLICATION POLICY

14.1.1 General Statement of Editorial Policy

It is anticipated that the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) will generate considerable new data relative to patients with anemia and hip fracture. The Steering Committee fosters and guides development of scientific reports originating from data obtained in the project. The scientific integrity of the project requires that all data from all Clinical Sites be analyzed study wide and reported as such. Thus, an individual center is expected not to report and publish data collected from its center alone. Development of sub studies or data bank studies dealing with specific analyses are encouraged. All presentations and publications of any data collected by the FOCUS Research Group are expected to protect the integrity of the main objectives of the overall project. Major findings are not presented prior to release of "mainline" results of the study by agreement of all FOCUS Clinical Site Directors. The Steering Committee determines the timing of presentation of mainline results (including papers on design and methods) and designation of the meetings at which they might be presented.

Publications are grouped into five general categories (see Section 14.1.2). Topics for consideration to be developed into publications are generated from questions or hypotheses that are submitted to the Steering Committee by investigators, study coordinators and other study-related staff. A writing group with a designated Chairperson is selected for each topic.

The Publications and Ancillary Studies Committee has primary responsibility for reviewing and approving all abstracts and all manuscripts on mainline findings, special laboratory studies, data bank or ancillary studies submitted for presentation or publication. Abstracts and manuscripts are also reviewed by the NHLBI according to existing procedures.

Investigators at all FOCUS Clinical Sites, the Clinical Coordinating Center (CCC), and the Data Coordinating Center (DCC) have equal status with regard to developing proposals, participating in such studies as approved by the Steering Committee, and collaborating in the development and publication of research papers based on study material. With the approval of the Principal Investigator, study coordinators and other staff at these centers are encouraged to participate in this process. The Management Committee has developed standards for regular evaluation of the submission and completion of these protocols. The Management Committee determines priorities for analyses among data bank study proposals which have been approved.

FOCUS Investigators at Clinical Sites, the CCC or DCC proposing studies that require the collaboration of CCC or DCC (e.g., Central Repository staff) contact the appropriate individuals prior to submission of a given proposal. The appropriate staff in the CCC and DCC participate in drafting the proposal, indicate willingness to participate, and identify sources of funding to support the level of effort required for the project.

The CCC and DCC Investigators are consulted in the development and analysis of protocols that require review of accumulated data or data on file at the CCC or DCC. The members of the CCC and DCC collaborate in designing and carrying out all FOCUS research.

14.1.2 Types of Research

Research and the resulting presentations and publications are grouped into the following categories:

1. Design paper(s) and reports on methodology.
2. Mainline findings.
3. Data bank studies.
4. Ancillary studies.
5. Independent studies.

Distinctions among these types of studies are given in Section 15.2. If possible, analysis of data may be conducted prior to the end of the FOCUS investigation and is strongly encouraged, so that the maximum information can be published from this study and so that the methods for evaluating and analyzing study data may be refined in preparation for later analyses.

14.1.3 Authorship

The first publication(s) pertaining to the fundamental goals of FOCUS involving patients enrolled in the study will list the members of the writing team as the authors with "the FOCUS Research Group" as the last author. An appendix listing the Principal Investigator and Co-Investigators will be included at the end of the manuscript's text. It is intended that there will be more than one publication concerning the mainline goals; all publications will list the writing team as the authors on behalf of the FOCUS Investigators.

14.1.4 Purpose of Procedural Guidelines

The procedures adopted by the investigators for use of study data are intended to protect the interests of all participants in the study, to assure that study data conform to the requirements of study design and are accurately presented, that authorship is appropriately acknowledged, that the text of each publication is well-written, to ensure that all investigators are aware of ongoing analysis projects, to avoid duplication of analysis projects and to ensure that publication or presentation of study data does not occur without the knowledge and approval of the Publications and Ancillary Studies Committee and the Steering Committee.

14.2 DESIGN AND METHODS REPORTS, MAINLINE FINDINGS, DATA BANK, ANCILLARY, AND INDEPENDENT STUDIES

14.2.1 Design Papers and Reports on Methodology

Manuscripts concerning the overall design, protocol, procedures, or organizational structure of the study that do not involve mainline findings or data collected on study patients may be published prior to the end of the study. Such preliminary publications will be developed and reviewed according to the same guidelines used for other reports of mainline findings.

Many public presentations about FOCUS that do not involve protocol data, special laboratory studies, data bank or ancillary study data (e.g., grand rounds talks concerning the study's general design and objectives) do not require formal preliminary review and approval by the Publications and Ancillary Studies Committee. However, if there is any doubt, investigators are asked to first consult with the Publications Committee indicating their intention to present the material, in order to avoid the premature release of study data or the inappropriate publication of confidential information.

14.2.2 Reports of Mainline Findings

A report on mainline findings is one addressing the fundamental goals of FOCUS or that involves protocol data -- such as changes in hemoglobin levels or functional status over time in anemic, hip fracture patients -- which cannot be released prior to the end of the study. These studies will summarize the findings based on the entire study population and will be written at the conclusion of the project. These reports must be reviewed and approved by the Publications and Ancillary Studies Committee and ratified by the Steering Committee.

14.2.3 Data Bank Studies

A data bank study uses data or specimens (including banked specimens) which are routinely collected on patients who are recruited and/or enrolled in the FOCUS. Analysis of these data are used to answer specific scientific questions. Data used in this research are not directly related to the fundamental goals of the study. Data bank studies must be approved by the Management Committee and ratified by the Steering Committee. All presentations or publications of data bank studies are to be reviewed following the procedures outlined in Section 14.4.

14.2.4 Ancillary Studies

An ancillary study uses supplementary data that are collected on patients who are recruited and/or enrolled in FOCUS, over and above the data collection required by the protocol. Such studies are restricted to consideration of a specific test technique or involve only the supplemental data collected on study cases and controls. Ancillary studies are reviewed and approved by the Management Committee and ratified by the Steering Committee prior to

initiation to ensure that they do not conflict with the main protocol. Review by the Publications and Ancillary Studies Committee is required for presentation or publication of an ancillary study.

14.2.5 Independent Studies

Independent studies of concern to FOCUS are studies conducted in potential patients who are not enrolled in the study, but data are collected at a Clinical Site. These data are not transmitted to the FOCUS Clinical Coordinating Center or Data Coordinating Center.

It is understood that each Clinical Site has the right to conduct studies which are independent of FOCUS in patients with who do not meet criteria for enrollment into the study. Independent studies of patients who meet eligibility criteria but are not enrolled in FOCUS must be reviewed by the Management Committee. Study investigators agree not to conduct independent studies which would compete with or have a detrimental effect on the conduct of FOCUS during the period of recruitment and follow-up.

14.3 GUIDELINES FOR PREPARATION OF PROPOSALS FOR DATA BANK AND ANCILLARY STUDIES

14.3.1 Data Bank and Ancillary Studies

Each proposal for an ancillary or data bank study should contain a brief description of the objectives, methods, analysis plans, significance of the study, and proposed collaborators. Full details should be given concerning any procedures to be carried out, such as bone marrow evaluations, exercise tests or psychological testing, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be carried out on patients or on banked specimens outside of the Clinical Site should be described. Mention should be made of the extent to which the data bank or ancillary

study requires extra clinic visits or prolongs the usual clinic visits. Information should be given concerning the extent to which the ancillary study require specimens in addition to those presently required by the protocol. If blood specimens are to be obtained from the patients or banked specimens are required, mention should be made of the number of specimens as well as a description of all procedures to be carried out on these specimens.

14.4 PROCEDURES FOR INITIATION AND APPROVAL OF STUDIES

14.4.1 Reports on Mainline Findings

Reports on mainline findings from FOCUS generally involve the collaboration of many investigators. Proposals for these reports are introduced and developed by any FOCUS Investigator or staff member with the approval of the Clinical Site Director. These reports are reviewed and approved by the Management Committee and ratified by the Steering Committee.

14.4.1.1 Submission of Proposals

Two copies of each proposal should be submitted to the Data Coordinating Center for inventory and transmission to the Management Committee. The Director of the DCC notifies the Investigator when the project is approved, disapproved or whether additional information is needed before a decision can be made.

14.4.1.2 Preparation of Mainline Reports

After approval of a proposed topic for a mainline report, members are elected or invited to serve on an ad hoc Writing Subcommittee and a Chairperson is chosen. These investigators work with the CCC and DCC staff to conduct the data analysis needed to investigate the question at hand and prepare a manuscript based on these findings. Every effort is made by the Subcommittee to consider and incorporate in this manuscript the comments and suggestions from

the Steering Committee. Often the Subcommittee members meet with staff from the CCC, DCC or other Clinical Sites for development of these papers.

14.4.1.3 Review and Approval of Abstracts and Manuscripts Prior to Presentation and Publication

Every study manuscript considered suitable for publication is submitted by the Chairperson of the Writing Subcommittee to the DCC for distribution to the Publications Committee. The Chair of the Publications and Ancillary Studies Committee is responsible for arranging and implementing review according to the following procedures.

1. The manuscript is forwarded promptly to at least two reviewers selected from the members of the Steering Committee or their associates, with the request to respond within two weeks with a detailed critical review of the manuscript. Outside reviewers are selected when appropriate.

2. Reviews are forwarded to all members of the ad hoc Writing Subcommittee with a request for appropriate revision and response.

3. The ad hoc Writing Subcommittee is expected to respond to the review in a reasonable period of time, forwarding to the CCC the revised manuscript and a letter commenting in detail on the points raised by the reviewers; DCC staff will distribute these materials to the Publications and Ancillary Studies Committee.

4. After review by the Publications and Ancillary Studies Committee, the DCC staff return the manuscript to the ad hoc Writing Subcommittee with final comments or suggested changes.

5. If acceptable to the study leadership (Management Committee), the completed manuscript is submitted by the Chairperson of the Writing Subcommittee to the

appropriate journal. A copy of the transmittal letter and copy of the manuscript are submitted to the DCC for distribution to the Steering Committee.

14.4.2 Data Bank Studies

14.4.2.1 Submission of Proposals

Data bank studies must be approved by the Management Committee and ratified by the Steering Committee. Before beginning a data bank project, a proposal initiated by one or more of the Investigators and/or their associates is submitted to the DCC for inventory and distribution to the Management Committee for consideration. The Director of the DCC notifies the Investigator when the project is approved, disapproved or additional information is needed before a decision can be made.

14.4.2.2 Conduct of Data Bank Studies

After approval is given by the Steering Committee, the Investigators (on the data bank project) work with the CCC and DCC staff to conduct the data analysis.

14.4.2.3 Priorities for Work

Because of the routine work load at the CCC and DCC, it is necessary to establish priorities for data processing and analysis. Therefore, the DCC staff conduct analyses on data bank studies in the order in which they have been approved or, as necessary, seek guidance from the Management Committee for determining priorities for analysis.

14.4.2.4 Authorship

After a data bank study proposal is approved by the Steering Committee, its research and development are the responsibility of the identified investigators on the project. Authorship decisions on data bank studies take into account the unique cooperative effort that has produced

the results. For clinical papers in particular, individuals from Clinical Sites, CCC, DCC and NHLBI staff have the opportunity to join writing teams when their contributions are appropriate. On the other hand, there will be papers of more limited scope which probably do not warrant a large number of authors. The following mechanism is utilized to determine authorship:

1. The lead author proposes a list of co-authors, based on the above guidelines.

2. The Management Committee reviews and approves, or makes recommendations regarding alterations in the proposed list of authors.

   The names of these investigators is followed by the designation "and

   FOCUS Research Group" on the byline.

14.4.2.5 Review and Approval of Abstracts and Manuscripts Prior to Presentation or Publication

The Publications and Ancillary Studies Committee reviews all data bank study abstracts and manuscripts prior to submission for presentation and publication. Recommendations are forwarded to the Management Committee for review and final decision. All abstracts must be received by the Publications and Ancillary Studies Committee members, all co-authors, DCC, and CCC at least two weeks prior to the submission deadline. Manuscripts prepared based on data bank studies must be submitted to the DCC at least one month (30 days) before the scheduled submission date. After review, the Publications Committee makes recommendations to the Management Committee in consultation with the DCC. The Director of the DCC notifies the authors and Steering Committee of the decision within one month of the receipt of a manuscript, within one week for abstracts. The approved manuscript or abstract is then submitted.

14.4.3 Ancillary Studies

14.4.3.1 Submission of Proposals

Ancillary study proposals are reviewed by the Management Committee and are ratified by the Steering Committee to ensure that the proposed study does not conflict with the primary goals of FOCUS.

Two copies of each proposal are submitted to the Data Coordinating Center for inventory and transmission to the Management Committee. The Director of the DCC notifies the Investigator when the project is approved, disapproved or additional information is needed before a decision can be made.

Abstracts and manuscripts are to be submitted for review prior to submission.

14.4.4 Independent Studies

Results of independent studies which are approved as acceptable by the Management Committee may be published or presented at the discretion of investigators initiating the independent study.

14.5 RELEASE OF FOCUS DATA OR SPECIMENS TO NON-FOCUS INVESTIGATORS

Requests for study results, study data, or banked specimens may be submitted by investigators who are not participating in FOCUS during the course of this investigation. These requests will arise primarily from colleagues and researchers who are interested in anemia. Each request should be submitted in writing and provide the same information as required for study data bank and ancillary studies submitted by FOCUS Investigators. The Management

Committee reviews each request and the following principles are addressed in determining the disposition of each request .

1. Overlap with the study major goals or approved data bank and ancillary studies.
2. The scientific importance of the request.
3. The efforts and costs of providing the information.
4. The willingness of the individuals submitting the request to accept the limitations, as specified by the FOCUS Management Committee, on the uses that can be made of the data and data analysis.

At least one month prior to the end of funding, the Data Coordinating Center staff will prepare data tapes and appropriate documentation for submission to the NHLBI Project Office. These tapes will not include personal identifiers of patients. The release of these data tapes will be based on the NHLBI Policy on Release of Data from Large Scale NHLBI Sponsored Studies.

14.6 CONFLICT OF INTEREST POLICY

14.6.1 General Principles

The FOCUS investigators have agreed to a policy on conflict of interest which has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The FOCUS investigators wish to endorse the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine (50) dealing with these issues, and seek to make this policy consistent with the record of that conference.

To address actual or perceived conflict of interest in FOCUS, the participating investigators voluntarily agree to abide by the guidelines described in the policy statement developed for FOCUS. See Exhibit 14-1 for a copy of the Conflict of Interest Statement.

14.6.2 Individuals to be Governed by These Guidelines

Members of the FOCUS Study Group who will be governed by these guidelines include the Study Chairman, the Director at each Clinical Site, key personnel in the Clinical Coordinating Center and Data Coordinating Center, and the Director of the ECG Core Laboratory. Co-Investigators and other staff who have major responsibility for enrollment, recruitment, follow-up or collection of data for FOCUS at Clinical Sites or ECG Core Laboratory will also be governed by these guidelines. The Principal Investigator for each FOCUS Center will submit a list of individuals who will be governed by these guidelines at the beginning of the study. The Director of each participating unit will review the guidelines with all appropriate staff prior to the start of patient recruitment and at least annually thereafter.

14.6.3 Time Period of the Policy

The guidelines set forth in this policy commence at the start of patient recruitment and will terminate at the time of initial public presentation or publication of the principal results. Investigators not privy to end point data who discontinue participation in the study during recruitment will be subject to these guidelines until their departure from the study.

14.6.4 Financial Guidelines

1. The investigators agree not to own, buy or sell stock or stock options during the aforementioned time period in any of the pharmaceutical companies or related medical equipment companies with products used in this study, or who have provided financial support for the study. In addition, the investigators agree not to have retainer-type consultant positions with these companies for the time period defined above.

2. The Clinical Coordinating Center will maintain conflict of interest statements updated annually from each investigator.

Activities not explicitly prohibited, but to be reported annually and maintained by the Clinical Coordinating Center include:

1. Ad hoc consultant relationships to companies providing products or equipment used in the study or providing financial support to the study.
2. Participation of investigators in any educational activities that are supported by the companies defined above.
3. Participation of investigators in other research projects supported by the companies defined above.
4. Financial interests in the companies defined above, over which the investigators has no control, such as mutual funds or blind trusts.

14.6.5 Reporting of Financial Disclosures and Other Activities

The investigators agree to update their financial disclosures and related activities as described above on an annual basis and submit these data to the Clinical Coordinating Center for storage. The Clinical Coordinating Center staff maintain the confidentiality of these records and prepare any reports indicating a potential conflict of interest for review by the Management Committee. In the case of actual or perceived conflict of interest, the Study Chairman brings it to the attention of the Management Committee, NHLBI Project Office, and the Data and Safety Monitoring Board.

14.6.6 Review of Policy Statement

The investigators agree to review these guidelines on an annual basis and take any additional steps to insure that the scientific integrity of the study remains intact.

14.6.7 Relationship to Institutional Policies on Conflict of Interest

Since existing policies on conflict of interest vary among participating institutions, in addition to the above policy, it is expected that investigators comply with the policies on conflict of interest which exist within their individual participating institutions (medical schools and hospitals). This is the responsibility of each individual investigator.

14.7 ACKNOWLEDGMENT OF NON-FEDERAL FUNDING

In the reports on major findings, data bank and ancillary studies, the financial support of all non-federal groups will be acknowledged at the end of each manuscript.

14.8 HUMAN SUBJECTS TRAINING

All FOCUS investigators and staff who have any contact with FOCUS patients, with health care providers treating FOCUS patients, with individual patients' FOCUS data or specimens must complete approved training in human subjects research and provide documentation of current training to the Clinical Coordinating Center annually.

EXHIBIT 14-1

CONFLICT OF INTEREST STATEMENT

FOR FOCUS INVESTIGATORS

CONFIDENTIAL

Except as noted below:

- I am not a part-time, full-time, paid or unpaid employee of any organizations:
- Whose products or services will be used or tested in the study under review, or (b) whose products or services would be directly and predictably affected in a major way by the outcome of the study;
- I am not an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations; and
- I do not have any financial interests or assets in any organizations meeting the above criteria, nor does my spouse, dependent children, nor organizations with which I am connected.

PLEASE COMPLETE THE APPROPRIATE BOX BELOW.

☐ NO RELEVANT INTERESTS OR ACTIVITIES.

☐ EXCEPTIONS ARE NOTED IN THE ATTACHED LETTER.

I will notify the Clinical Coordinating Center Principal Investigator promptly if:

- A change occurs in any of the above during the tenure of my responsibilities, or
- I discover that an organization with which I have a relationship meets the criteria for a conflict of interest.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

_____ _____

Investigator (type name) Signature

_____

Date

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