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1) Specific Aims

The overall goal 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. The specific aims of the study are:

a) Primary Aim:

To determine if a 10 g/dL transfusion strategy is associated with improved ability to walk ten feet across a room without human assistance 60 days after surgery compared to a symptomatic transfusion strategy.

b) Secondary Aims:

- i) To determine if a 10 g/dL transfusion strategy is associated with lower risk of postoperative myocardial infarction or death after surgery compared to a symptomatic transfusion strategy.
- ii) To determine if a 10 g/dL transfusion strategy is associated with a decreased risk of postoperative 30-day and long term mortality compared to a symptomatic transfusion strategy.
- iii) To determine if a 10 g/dL transfusion strategy is associated with improved lower extremity function and instrumental activities of daily living 30 and 60 days after surgery compared to a symptomatic transfusion strategy.
- iv) To determine if a 10 g/dL transfusion strategy is associated with fewer patients remaining in a nursing home 60 days after surgery compared to a symptomatic transfusion strategy.

c) Tertiary Aims:

- i) To determine if a 10 g/dL transfusion strategy is associated with a decreased risk of in-hospital postoperative non-infectious morbidity compared to a symptomatic transfusion strategy. Specific morbid outcomes to be assessed are delirium, stroke, and thromboembolism.
- ii) To determine if a 10 g/dL transfusion strategy is associated with an increased risk of in-hospital postoperative pneumonia.
- iii) To determine if a 10 g/dL transfusion strategy is associated with decreased risk of composite outcome of 30-day mortality, myocardial infarction, pneumonia, stroke, and thromboembolism.
- iv) To assess the frequency of selected medical errors in a frail, elderly population.
- v) To identify patient characteristics that are predictive of successful rehabilitation.

2) Background and Significance

Blood transfusions should be prescribed only after a careful consideration of the risks versus the benefits of the therapy. Recent studies document an extremely low rate of adverse effects, which includes errors of administration, transmission of infectious diseases, volume overload and others. The well accepted benefit of blood transfusion principally relates to the improvement of oxygen carrying capacity. However, no large scale randomized controlled trials exist in surgical

patients that characterize these clinical benefits and the associated risks of transfusion. This scientific uncertainty has led to variation in transfusion practice which has been demonstrated in surgical patients. Blood transfusion is expensive and widely used. In the US alone, there are over 13 million units of allogeneic blood transfused per year at a cost of over 3.4 billion dollars.

3) Patient Population

- a) 2,600 patients with cardiovascular disease or cardiovascular risk factors and acute hip fracture undergoing surgical repair.
- b) Hemoglobin level less than 10 g/dl from the end of surgery to the 3rd postoperative day.
- c) Patients are excluded for multiple trauma, active symptoms from anemia at time of randomization, and refusal of blood transfusion for religious or other reasons.

4) Treatments

- a) 10 g/dL Transfusion. Immediately receives 1 unit of packed red cells. A post-transfusion hemoglobin level is measured, and the patient receives as much blood as is necessary to keep the hemoglobin level above 10 g/dL.
- b) Symptomatic Transfusion. Transfusion is withheld until the patient develops symptoms from anemia that the surgeon believes would be treated with blood transfusion (i.e., chest pain or ECG changes thought to be ischemic, congestive heart failure, unexplained tachycardia or hypotension unresponsive to fluids, unable to get out of bed 3 days after surgery) or until the hemoglobin level falls below 8 g/dL. Transfusion is permitted, but is not mandatory, if the hemoglobin level falls below 8 g/dl. Patients who have a history of dementia will receive a transfusion when the hemoglobin level falls below 8g/dL because of the difficulty in identifying symptoms of anemia. Enough blood is given to relieve symptoms or to keep hemoglobin level above 8 g/dL.

5) Assignment to Transfusion Group

- a) Randomization by coordinating center using toll free (800) telephone number.
- b) Randomization stratified by clinical center.

6) Blinding

- a) Assignment will not be blinded.

7) Primary Outcomes

- a) At 60 days after surgery, death or inability to walk 10 feet or across the room (independently or with the assistance of a mechanical aid).

8) Secondary Outcomes

- a) Myocardial infarction or death.
- b) 30-day and long term mortality.
- c) Lower extremity function and instrumental activities of daily living 30 and 60 days after surgery.
- d) Nursing home residence 60 days after surgery.

9) Tertiary Outcomes

- a) Non-infectious morbidity including delirium, stroke, and thromboembolism.
- b) Postoperative pneumonia.
- c) Composite outcome of 30-day mortality, myocardial infarction, pneumonia, stroke, and thromboembolism.
- d) Selected medical errors.
- e) Patient characteristics that are predictive of successful rehabilitation.

10) Outcome Detection and Adherence to Protocol

- a) Daily in-hospital review of hospital chart by study personnel.
- b) Electrocardiogram prior to surgery, postoperative day 1 and 4 days after randomization. Troponin level preop, prior to randomization, day 1 and day 4 post randomization. Troponin measured by Troponin Core Laboratory.
- c) Telephone contact by personnel from study chairman's office at 30 and 60 days after surgery.
- d) Vital statistic registry search for mortality.

11) Outcome Classification

- a) In-hospital mortality and secondary outcomes retrieved by staff at each clinical site. ECG and MI classification by ECG Core Laboratory.
- b) Post discharge vital status determined by telephone contact at 30 and 60 days and the National Death Index and Statistics Canada.

12) Primary Analysis

- a) Intention to treat.
- b) Comparison of primary outcome using chi square test with one degree freedom.

13) Budget:

- a) \$950 plus indirect costs per case randomized.

14) Time Line

- a) 6 months planning and organization.
- b) 3.5 years patient enrollment and data collection.
- c) 1 year analysis.

15) Sponsor

- a) National Heart, Lung, and Blood Institute.