Does Plasma Reduce Bleeding in Patients Undergoing Invasive Procedures

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***Title of Project*:**	**Does Plasma Reduce Bleeding in Patients Undergoing Invasive Procedures**
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1. Purpose/Specific Aims

Patients with prolonged clotting times (INR ≥1.5), who are to undergo invasive procedures (e.g., central venous catheter placement, endoscopy, bronchoscopy, cystoscopy, angiography), may be at increased risk of bleeding for which physicians commonly order pre-procedure plasma transfusion. However the efficacy of prophylactic plasma transfusion has not been established. This pilot study will determine the feasibility and optimal study design of a large randomized NIH-Defined Phase III Clinical Trial that will provide critical clinic evidence to guide transfusion practice.

1.1 Objectives

Objective 1: To evaluate the feasibility of a research protocol that will lead to a large-scale clinical trial designed to evaluate the effectiveness of plasma in patients with prolonged INR undergoing an invasive procedure.

- To determine the eligibility and enrollment rate into the study protocol
- To assess the patient characteristics of patients enrolled in this trial.
- To determine adherence rates for the plasma transfusion protocol and test methods to minimize protocol violations.
- To establish frequencies of bleeding, transfusion associated cardiac overload (TACO), and transfusion related acute lung injury (TRALI) in patients enrolled in this pilot study to calculate sample size for large definitive trial.

Objective 2: To compare the risk of major bleeding and complications in patients with an INR of 1.5 to 2.5 undergoing an invasive procedure who are randomly allocated to receive plasma versus no treatment.

- To compare the risk of major bleeding defined as drop in hemoglobin level 2 g/dL or greater, mean hemoglobin concentration, and use of red blood cell transfusion in patients randomly assigned to plasma compared to no treatment.
- To determine if use of plasma is associated with higher rate TACO, TRALI, infection, transfer to ICU and ICU days, mortality, or length of hospital stay compared to no treatment.

1.2 Hypotheses

The primary study hypothesis is that prophylactic plasma transfusion in patients with INRs between 1.5 and 2.5 will reduce post procedure major bleeding (drop in hemoglobin of 2 g/dL or greater) compared to patients who do not receive plasma.

2. Background and Significance

Plasma from whole blood is a frequently administered blood product,[1,2] and its usage in the U.S. approaches 4 million units transfused annually.[3] Recent data demonstrate that relative to red blood cell transfusion, the number of plasma units transfused in the United States is higher than in other countries with advanced medical care.[1,2] Plasma may be used to manage active bleeding (e.g. trauma) or prophylactically to reduce risk of bleeding. The transfusion of plasma prior to an invasive procedure in order to correct a perceived bleeding risk is common, and in a recent survey of plasma transfusion approximately 30% of requests for plasma were for patients scheduled to undergo an invasive procedure.[4] However, there is no definitive clinical trial evidence to substantiate this practice.

Fresh frozen plasma (FFP) contains all of the coagulation factors and proteins present in whole blood but slightly diluted by the anticoagulant solution used to collect the blood. Technically, fresh frozen plasma is plasma placed in an -18º to -30º C freezer within 8 hours of phlebotomy. Each unit is derived from single donor and is about 250cc. Frozen Plasma (PF24) is plasma that is frozen within 24 hours of phlebotomy and is often used interchangeably with fresh frozen plasma. Frozen plasma 24 has the same levels of clotting factors as fresh frozen plasma except for factor VIII levels, which are 65% to 80% of normal levels. Thawed Plasma is made by thawing fresh frozen plasma or frozen plasma 24 and then storing it up to 5 days at 1-6 º C. All factors remain stable at refrigerator temperatures except factor V that declines to approximately 80% of normal and factor VIII to 50% normal. Thawed plasma is used interchangeably with fresh frozen plasma or frozen plasma 24. This protocol uses "plasma" to refer to fresh frozen plasma, frozen plasma 24 or thawed plasma.

In general, hemostasis is considered adequate if the factor concentrations are 25% to 30% of normal.[5] Since plasma volumes are 40 cc/Kg, a dose of 10-15cc/kg is required (assuming coagulation factor level equal to 0). Thus, three to five units are required in the average patient.

In general, each unit of plasma is infused over 30-60 minutes (3-6cc/kg/hour) in patients with reasonable cardiac function and up to a maximum of 4 hours per unit in patients with reduced left ventricular function (1 cc/kg/hour).

Clinicians usually assess blood coagulation (and hence the need for plasma) by the results for in vitro tests of prothrombin time (PT), activated partial thromboplastin time (PTT), and platelet count. The prothrombin time evaluates the extrinsic pathway and may be prolonged with Vitamin K deficiency due to use of warfarin, poor nutrition, antibiotics, liver disease, or many other less common disorders. The prothrombin time is also reported as INR (International Ratio), which adjusts for different sensitivities of reagents used for the test. A normal INR is 1.0 and INR from 2.0-3.0 is in the therapeutic range for patients treated with the anticoagulant warfarin (Coumadin). Patients with INR from 1.5-2.5 may be at increased risk of bleeding especially after an invasive procedure. The PTT is used to evaluate the intrinsic system and to monitor treatment with unfractionated heparin. The PTT is prolonged in patients with factor deficiencies of the intrinsic system.

When deciding to use plasma prophylactically or prior to an invasive procedure, the clinician makes several assumptions. The first assumption is that elevated laboratory measures of coagulation such as prothrombin time and INR confer an increased risk of bleeding. However, prothrombin time and INR were never validated for use in this setting. Highlighting this point, a recent systematic review assessed whether abnormalities in pre-procedure coagulation tests correlated with an increased risk of bleeding.[6] Analysis of 24 observational studies and 1 RCT included nearly 2000 procedures performed on patients with abnormal coagulation studies and concluded that there is not sufficient data to support PT and INR as predictors of bleeding risk.

A second assumption that the clinician makes when deciding to transfuse plasma is that administration of plasma will improve the INR value and thereby reduce the procedure's risk of bleeding complications. In fact, there is surprisingly little evidence to support the ability of plasma to correct an abnormal INR.[7,8] Given that the INR of plasma can be as high as 1.3, transfusion will have little effect on a minimally elevated INR. This point is emphasized by a prospective study evaluating the effectiveness of transfusing plasma to correct an increased INR in patients with a mildly prolonged PT (13.1 to 17 seconds).[9] Of 121 patients studied, <1% normalized their INR and only 15% demonstrated improvement at least halfway to normal. It is important to emphasize that pre-procedural doses of plasma are often inadequate to consistently correct coagulation factor deficiencies. Highlighting this point, a recent study of plasma use in the critical care setting observed that prophylactic transfusions were often given at 10 mL/kg or under, while evidence suggests that correction of low coagulation factor levels may require plasma doses as high as 30 mL/kg (approximately 8 units).[10,11] Data from analysis of plasma use in 10 hospitals also shows that plasma is usually under dosed (see below).[12]

Given the paucity of high quality evidence to guide prophylactic transfusion of plasma, in 2010 the AABB published practice guidelines to assist practitioners.[2,13] Importantly, no studies of nonsurgical invasive procedures met review inclusion criteria. Acknowledging this lack of data regarding peri-procedural management of patients with abnormal coagulation parameters, the Society of Interventional Radiology recently published consensus guidelines.[14] These guidelines recommend that in the absence of warfarin treatment or liver disease, pre-procedure INR testing be conducted only prior to procedures with moderate to high bleeding risk. In patients scheduled

to undergo moderate or high bleeding risk procedures, these guidelines recommend that the INR be corrected to <1.5, although this recommendation was derived by Delphi consensus of expert practitioners not high quality evidence from randomized clinical trials.[14]

We know of three clinical trials that evaluated the use the plasma prior to an invasive procedure outside the operating room.[6,15,16] The only published trial found no difference in bleeding in 72 patients with either prolonged protime or thrombocytopenia undergoing percutaneous dilatational tracheotomy.[17] The other two trials did not successfully recruit (ICU patients (N=81 of 400)[18] and hepatic procedures (N=3 of 1172). This experience highlights the need to expand eligibility criteria and for a pilot study to demonstrate feasibility.

Clinicians must also consider the adverse effects of plasma. The risks of transfusion virus transmission are similar to a red blood cell transfusion, which has decreased greatly throughout the past two decades.[19,20] Currently, the transmission of infectious diseases by blood is rare. However, non-infectious risks are more common. Transfusion associated circulatory overload (TACO) is of greatest concern, and may be under-recognized. A prospective surveillance study of the risk of TACO in patients receiving plasma found a 5% incidence.[21] A similar risk has been reported with red blood cell transfusion, also estimated to be from 1% to 6%.[22-24] The per unit risk of transfusion related acute lung injury (TRALI) associated with plasma is declining and is estimated to be on the order of 1:12,000.[25] Recalling that pre-procedural plasma is typically under-dosed, it stands that larger volumes of plasma would confer increased risk to patients receiving plasma in order to correct a perceived coagulopathy prior to a procedure. Thus it is critical to define whether the current practice to provide plasma when correctly dosed is doing more harm than good or whether this risk can be easily managed with a prophylactic dose of diuretic.

Despite the absence of data, there are several reasons why clinicians frequently use plasma prior to invasive procedures. First, a markedly prolonged coagulation tests clearly increase the risk of bleeding so that it is reasonable to anticipate that modest INR (1.5-2.5) may also increase risk of bleeding. Second, it is possible that plasma may benefit a subset of patients with modest prolongations of PT/INR such as those with thrombocytopenia or platelet dysfunction. Third, there is a common concern of medicolegal consequences of performing a procedure in the face of an "abnormal" coagulation test result. Fourth, there are no high quality trials that prove that it is beneficial and/or safe not to give plasma. Supporting the rationale to give plasma is findings from plasma epidemiology study that shows about 20% of patients have a drop in hemoglobin greater than 2 g/dL after procedure.[26] Thus, despite the ongoing campaign to reduce plasma use and the generation of many sets of clinical guidelines suggesting its lack of efficacy without clinical trial evidence, it may be that the problem is not that plasma is not indicated but rather the dose of plasma is too low and ineffective [9,12]

Conclusions:
Plasma is widely used before invasive procedures in patients with moderately prolonged INR with the expectation that bleeding will be prevented or reduced. Yet there are no randomized clinical trials that demonstrate plasma is efficacious… using the proper dose….or prove that is safe not to administer plasma. Furthermore, there are no trials that describe how common or clinically important are the side effects of plasma. Thus, a large pragmatic clinical trial is needed to definitively establish or refute the efficacy and safety of properly dosed plasma. Only a high

quality clinical trial will provide the essential evidence to demonstrate to clinicians that the risks of plasma outweigh the minimal if any hemostatic benefits in patients with moderately prolonged INR undergoing an invasive procedure OR show that clinically significant bleeding can be reduced with appropriately dosed plasma and that infrequent side effects like TACO than can be easily managed with a dose of a diuretic. Because of the challenges in the past of enrolling patients into similar trials it is essential that a pilot trial be performed which provides the necessary and sufficient experience needed to plan and successfully complete a large multicenter trial that provides the essential evidence to guide the transfusion of plasma.

3. Research Design and Methods

We will perform a randomized clinical trial using simplified inclusion criteria along with minimal exclusions to ensure implementation of a pragmatic study whose results will be widely generalizable.

Eligible study subjects will be randomly allocated to either receive either plasma transfusion prior to the invasive procedure, or to no treatment. Treatment arm will be assigned according to a 1:1 ratio to plasma or no treatment using a permuted block design with variable block sizes of 4 and 6 and stratified by clinical site and liver disease via a predetermined randomization table. The treatment allocation is provided in real time, using the web based study application. Treatment assignment is not masked.

Outside of pre-procedure plasma transfusion, all medical care is per treating physician. Each of the transfusion strategies is consistent with medically established guidelines for the study population, patients with moderately elevated INRs. Study subjects will be followed (via medical record review) through the hospitalization.

At time of randomization, a baseline (within 24 hours prior to randomization and plasma transfusion) hemoglobin level and INR will be obtained. Those allocated to plasma will be transfused a target dose of 15 cc per kilogram to a maximum dose of 5 units. Hemoglobin levels and INRs will be collected following the procedure and on the following 2 days (if still in the hospital). In the rare instances that these laboratory tests have not been ordered for clinical reasons, they will be ordered as research tests.

Detailed information related to bleeding and plasma complications within the 2 days following the procedure will be abstracted from the medical chart (transfusion of all blood products including red blood cells, plasma, platelets and cryoprecipitate), as will hemoglobin levels and all red cell or fresh frozen plasma transfusions within 7 days after randomization. Post procedure medical events will be recorded.

If, within the 2 post procedure days, the subject experiences any new cardiopulmonary symptoms, relevant sections of the medical record, including progress notes, relevant consults, the official interpretation of chest x-rays or CT scans, laboratory studies (BNP, troponin, and electrocardiograms), and treatments including diuretics, will be copied. These records will be redacted of all personal health identifiers (PHI) and sent to the Outcome Classifications Committee. The Outcome Classifications Committee, comprised of two of the study co-investigators masked to treatment allocation, will adjudicate occurrence of TACO and TRALI,

medically important outcomes which are susceptible to misclassification and bias in this unblinded clinical setting.

3.1. Duration of Study

The enrollment phase of the study will be 28 months, and each subject entered into the trial will be followed through the hospitalization, for up to 30 days. A total of 110 subjects will be enrolled. It will take 3 years to complete the study.

3.2 Study Sites

There are 4 clinical sites in the pilot study: Robert Wood Johnson University Hospital (PI: Jeffrey Carson, Co-investigators Lauren Hogshire and Claire Phillip), Johns Hopkins University Hospital (PI: Paul Ness), University of Pittsburgh Medical Center- Presbyterian Hospital (PI: Darrell Triulzi) , University of Washington Medical Center (PI: Terry Gernsheimer, Monica Pagano), and Baylor St Luke's Medical Center (PI: Arthur Bracey). Each clinical site will have a team composed of PI and clinical site coordinator.

The University of Pittsburgh under the direction of Maria Brooks will generate the randomization table used to allocate treatment assignment.

3.3 Sample Size Justification

Pilot: For the enrollment, adherence and event rates needed for planning and feasibility analyses, we determined that the width of a 90% confidence interval should be 0.10 or less for true proportions equal to 0.10 (or equivalently 0.90) and 0.15 or less for proportions equal to 0.30 (or equivalently 0.70). With 110 persons enrolled in the pilot trial, the 90% confidence intervals for estimated proportions equal to 0.10, 0.20 and 0.30 will have widths 0.10, 0.13, and 0.15, respectively, based on data from the combined sample, and widths 0.15, 0.19, and 0.22, respectively, based on data from one treatment arm (i.e. n=55). The 90% confidence intervals for estimated means for continuous measures will have precision +/- 0.16*SD for the combined sample and +/- 0.22*SD for each treatment arm. A pilot trial with a total sample size of N=110 will have 90% power to detect a difference of 0.62 SD between the mean hemoglobin change between the two assigned treatment groups. For example, estimating that hemoglobin change has a SD of approximately 1.0 g/dL, this pilot trial would have 90% power to detect difference of 0.62 g/dL in the change of hemoglobin level from baseline to the nadir between the two assigned treatment groups.

3.4 Subject Selection

3.4.1 Inclusion Criteria

A patient is eligible for enrollment when the following criteria are met: 1) 21 years of age or older, 2) an INR between 1.5 and 2.5, 3) undergoing an invasive procedure at the bedside, endoscopy laboratory, or in radiology.

These criteria will enroll a broad, generalizable group of study subjects with moderately prolonged INRs in whom many clinicians transfuse plasma prior to an invasive procedure with the expectation that this will lower the risk of bleeding. The lower range of INR (1.5) closely approximates that recommended by Society of Interventional Radiology and the upper range (2.5) is below that for which plasma is clearly required. Recent data confirm that a large proportion of plasma is given to patients with INRs in this range and thus reflects current practice.[26]

3.4.2 Exclusion Criteria

Patients will be excluded if any of the following criteria are met: 1) undergoing a surgical procedure in the operating room; 2) active bleeding; 3) undergoing a procedure involving or proximal to the central nervous system or spinal cord; 4) cardiac catheterization, 5) using 4 factor plasma concentrates 6) using direct factor X inhibitors and other anticoagulants for which plasma will not correct prolonged INR; 7) platelet count less than 40,000/ul, 8) congenital coagulation disorders; 9) acquired disorders (i.e., lupus anticoagulant) for which plasma will not correct the disorder; 10) women who are pregnant; 11) Patients on intravenous heparin that is not discontinued $\geq$ 4 hours prior to the procedure and; 12)Patients unwillingness to consider blood transfusion.
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Patients undergoing surgical procedures in the operating room are excluded because blood loss will occur in all these patients regardless of their coagulation status and change in hemoglobin level will not be as useful an outcome compared to patients undergoing more minor procedures that would not ordinarily lead to significant bleeding. Patients undergoing procedures proximal or involving the central nervous system are excluded because even minimal blood loss could be dangerous. Patients using anticoagulants, for which plasma does not correct INR, as well as those receiving 4 factor plasma concentrates, are excluded. Patients undergoing cardiac catheterization are excluded since they received multiple anticoagulants and platelet inhibitors as part of the procedure and patients with platelet counts less than 40,000/ul are excluded since these patients may be at greater risk of bleeding.

Patients receiving platelet transfusions prior to the procedure are not excluded. However, since a platelet transfusion includes about 300 ccs of plasma, the INR level confirming eligibility must be performed after the platelet transfusion.

3.4.3 Heparin Treated Patients

In patients on intravenous heparin, it is not possible to stop heparin, check an INR, consent, and administer plasma prior to procedure. Given the minimal effect of heparin on INR, patients will be eligible for the trial if the INR is between 1.5 and 2.5 while

receiving heparin. In patients on intravenous heparin, the medication must be stopped > 4 hours prior to the procedure and plasma will not be started until 4 hours after discontinuation of heparin. An INR will be checked 4 hours after stopping heparin but plasma may be administrated without waiting for the results of the INR off heparin. Heparin may be restarted after the procedure at the discretion of the clinical team.

4. Study Variables

4.1 Independent Variables or Interventions

4.1.1 Interventions

Plasma: Patients randomized to plasma will receive the standard target dose of 15cc per Kg (acceptable range 10-20 cc/Kg) to maximum of five units up to four hours prior to the procedure (and 6 hours in patients with documented or clinically suspected reduced ejection fraction). We will limit the maximum dose of plasma to five units since this emulates what clinicians often do and the concerns about fluid overload from the administration of larger doses of plasma. The attending physician will determine the rate of administration of the plasma.

No Treatment: We will compare to the alternative, which is no treatment prior to procedure

There are several procedures in place to ensure adherence to the assigned treatment arm. Following randomization, the subject's chart will be labeled in the progress note to indicate the assigned transfusion strategy. The Clinical Site Coordinator will contact the attending, house staff, fellow, and nurse to inform them of the patient's assignment and review the protocol. The blood bank will be notified of the subject's treatment assignment and asked to notify study personnel if plasma is ordered for a patient assigned to the no-treatment arm. If administration of plasma is a violation of the protocol, study staff will contact the ordering physician to discuss transfusion plans and to clarify the study protocol. However, study staff does not approve or disapprove the transfusion and will not delay emergent transfusion; the treating physician controls care.

4.2 Dependent Variables or Outcome Measures

Outcomes Assessing Trial Performance and Feasibility:

The primary feasibility outcome will be enrollment rate, overall and by center. Secondary outcomes will include a) Eligibility rates overall and by center; b) Adherence rates for the plasma protocol, overall and by center; c) Frequencies of proposed study outcomes. With the proposed sample size, this pilot study will only provide an approximation of rates. d) Patient characteristics of patients enrolled in this trial including the procedures the patients underwent and the location of the procedure (i.e., ICU, radiology)

Secondary Outcomes Assessing Treatment Effectiveness and Safety:

During the 2 days following randomization, we will compare: 1) Major Bleeding. 2) Mean Change in Hemoglobin Level: This continuous variable will be much more sensitive measure of bleeding and will be the primary clinical outcome in the pilot study. 3) Red blood cell transfusion: We will compare the percentage of patients and number of red blood cell units transfused between the two arms. 4) Transfusion Associated Cardiac Overload (TACO) i.e., congestive heart failure. 5) Transfusion Related Acute Lung Injury (TRALI). 6) Change in INR. We will determine the change in INR from baseline to measurement after procedure, day 1, and day 2. We also will determine the frequency in which the post transfusion INR is less than 1.5. 7) Other outcomes: sites and characteristics of major bleeding, all cause in-hospital mortality, length of hospital stay from time of randomization to discharge, pneumonia or blood stream infection, transfer to intensive care unit, and number of days in intensive care unit.

We will also compare plasma and red cell transfusions received between the treatment arms during the 7 days following the procedure.

The following criteria will be used to define the secondary outcomes:

Major Bleeding: Major bleeding will be defined as decline of 2 g/dL or more in hemoglobin level from the baseline to nadir hemoglobin level within 2 days of the procedure. In patients receiving red blood cell transfusions, the change in hemoglobin level (baseline level minus the nadir) will be increased 1 g/dL for each unit transfused.

Mean Change in Hemoglobin Level: Mean change in hemoglobin level within 2 days will be defined as the difference between the hemoglobin level before and the nadir hemoglobin within 2 days of the procedure. In patients receiving red blood cell transfusions, the change in hemoglobin level will be increased 1 g/dL for each unit transfused.

Transfusion Associated Cardiac Overload (TACO)*:* TACO is equivalent to congestive heart failure in patients receiving transfusion. Congestive heart failure will be diagnosed by the Outcomes Classification Committee. The essential components are: 1) Clinical symptoms of heart failure (New or worsening symptoms such as dyspnea, orthopnea and two or more signs including edema, pulmonary crackles, tachypnea, S3 gallop, radiographic evidence of worsening heart failure) 2) Need for additional/increased therapy (Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure or initiation of intravenous diuretic, inotrope, or vasodilator therapy and 3) No other non-cardiac etiology for signs or symptoms is identified.

Transfusion Related Acute Lung Injury (TRALI*):* TRALI will be diagnosed by the Outcomes Classification Committee using the Canadian Consensus Conference definition.[27] The criteria include 1) acute onset, 2) hypoxemia defined as $PaO_2/FIO_2 <$ 300 or $SpO_2 < 90\%$ on room air, 3) bilateral infiltrates on chest radiograph, 3) no evidence for circulatory overload, 4) no preexisting acute lung injury before transfusion,

5) occurs within 6 hours of transfusion, and 6) no temporal relationship to alternative risk factor for acute lung injury.

Pneumonia and Blood Stream Infection*:* The CDC criteria will be used for clinically defined pneumonia based on two or more serial x-rays and blood stream infection. [28,29]

Length of stay, Intensive Care Unit days: The number of days post randomization that patient is in the hospital, along with the number of days post randomization the patient is in ICU, if applicable, will be collected.

4.3 *Chart Review Selection*

Local study staff will abstract data for each potential study subject from the medical record to assess eligibility and patient demographics. The subject will be identified with a unique sequential study identification number. If the subject has any of the exclusion criteria, or the treating physician does not agree to enroll subject, or consent is not obtained, no further data will be collected. If a consented subject does not undergo a procedure (i.e., consent is obtained in anticipation of a procedure which does not occur or a procedure is canceled) no data other than the INR level will be collected.

For each consented patient who undergoes a procedure, abstracted data will include: baseline medical status and comorbidities; pre-procedure INR, hemoglobin levels and plasma transfusions; specific procedure performed and setting; post procedure INR, hemoglobin levels, plasma, and red blood cell transfusions; and the clinical data to determine the study outcomes listed above. Other than dates, PHI will not be collected.

4.4 Risks of Harm

Transmission of infectious diseases (e.g., hepatitis B, hepatitis C, HIV) via plasma transfusion is less than 1 in 10,000. The estimated risk of transfusion associated circulatory overload (TACO) is 5% and transfusion related acute lung injury (TRALI) is estimated to be on the order of 1:12,000.

The two transfusion strategies are within medically established guidelines for the study population. No compelling evidence shows one approach to be better than the other, i.e., a state of equipoise exists. Physicians commonly believe that patients with moderately elevated INR levels are at increased risk for bleeding following an invasive procedure, and that plasma transfusion will mitigate that risk. However there is no medical evidence to support this use of plasma. Furthermore there are risks associated the plasma transfusion including TACO and TRALI which could outweigh any potential benefit. Thus, clinical risks to study subjects above those of usual practice are not a consideration. An independent Data and Safety Monitoring Board (DSMB) will monitor the study to assure patient safety.

There are no other alternative treatments.

4.5 Potential for Benefit

There are no direct benefits to the study participants. This pilot study will be the first step in attaining the essential clinical trial data to understand the true risk of bleeding, and the impact of plasma on that risk, for patients with a moderate elevation in INR who undergo invasive procedures.

5. Subject Recruitment and Enrollment Considerations

5.1 Subject Recruitment

Potential study subjects are likely to be identified in the intensive care units where bedside procedures are performed or via a scheduled procedure by interventional radiologists or gastroenterologists and by blood banks. Study personnel will present the trial to the medical staff prior to the initiation of patient recruitment. Only patients whose treating physician has agreed to cooperate with the study protocol will be considered for participation. Study staff will screen the medical records of patients identified in these settings (details below) to determine those who have an INR measurement in the study range and who are eligible for the study.

1) Intensive Care Unit: Many bedside procedures are performed in the intensive care unit and plasma is often administered if the INR is prolonged. We will identify collaborators in all the major ICUs in the hospital and seek help in identifying patients eligible for the trial. We will request that someone from the ICU team contact the research nurse with potential subjects. In addition, the research nurse will visit each ICU daily to identify potential patients for the trial. In the ICU setting, consent will be sought for all potential subjects likely to undergo a bedside procedure (as compared to scheduled for the procedure), as the majority of these patients may require that the procedure be performed (e.g., insertion of a swan ganz catheter) urgently.
2) Interventional Radiology and Endoscopy Laboratory: A prothrombin time/INR along with PTT, and platelet count are required prior to performing most procedures. We will review daily the patients scheduled for a procedure. In any inpatient with an INR between 1.5 and 2.5, we will contact the patient's attending physician and request permission to consent the patient. We will also confirm that the interventional radiologist or gastroenterologist/pulmonologist is willing to follow the transfusion protocol and perform the procedure if the patient is enrolled in the trial.
3) Blood Bank: The research nurse will telephone the blood bank twice daily to determine if plasma has been ordered for a patient and the medical record will be reviewed to determine eligibility for the trial.

5.2 Consent Procedures

The clinical site coordinator will identify him/herself to the patient as a member of the research team and request permission to tell the patient about the study. The coordinator will describe the purpose of the study and the two transfusion strategies (plasma transfusion or no transfusion) and the collection of medical information. If the patient agrees to participate in the trial, the signed IRB approved consent form will be placed in the medical record and the coordinator will keep make a copy to keep with the subject's study file.

To minimize placing undue pressure on the patient to agree to participate, the person obtaining consent will not be directly involved in the patient's medical care. It will be emphasized that consent is voluntary, that the medical care the patient receives will not be influenced by his or her decision, and that, should the patient agree to participate, he or she is free to withdraw from the study at any time. After the study has been introduced, the coordinator will leave a copy of the unsigned consent with the patient for consideration. The coordinator will arrange to return at a time convenient for the patient to determine his or her participatory status. If the patient agrees, he or she will sign the consent at that time.

5.3 Subject Costs and Compensation

The trial is being performed under usual care conditions and there are no costs to the subjects for study participation. In the (rare) instance a protocol required hemoglobin or INR has not been ordered by the treating physician, the cost of the test will be covered by the trial.

There is no compensation to study subjects.

6. *Data Handling*

Study data will be collected and managed using REDCap electronic data capture tools[30] hosted at Rutgers Robert Wood Johnson Medical School. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Each study subject will be assigned a unique sequential study identification number. Local site staff will enter the de-identified study data directly onto the web application via a secure web connection with authentication, using the study number to identify the individual subject. Other than dates, the study does not collect PHI. The REDCap entry module is programmed to have real-time data validation and integrity checks. Access to the electronic data is permitted on a need to know basis through user rights assigned by the coordinating

center at Rutgers Robert Wood Johnson Medical School. Staff at the coordinating center will download the data from the web application into SAS software and perform all data analyses.

The study-wide de-identified database will not be destroyed.

All medical records that are copied as source documentation for adjudication of TACO and TRALI will be labeled with the study identification number and striped of identifiers.

Only the staff at the local site will have the link to PHI for the subjects that are enrolled at that site.

7. Statistical Analysis

Eligibility and Enrollment: The feasibility of enrollment will be evaluated by determining 1) the number of patients that undergo invasive procedures with an INR between 1.5 and 2.5; 2) the number of patients that meet the eligibility criteria for the trial 3) the proportion of eligible patients that are willing to be randomized and the proportion of eligible patients who are enrolled in the trial. These proportions will be estimated directly as the observed ratio of numbers of patients, and 90% confidence intervals will be calculated to understand the likely range of values for a larger study with a comparable research protocol. For each center, the reasons why patients are not enrolled including frequencies of individual exclusions and the proportion of patients declining participation will be described.

Adherence: Adherence rates for the plasma protocol will be ascertained as the proportion of enrolled patients who adhere to the intervention as assigned and the proportion of patients who complete the follow-up evaluations for each assigned group, overall and by center. Estimated proportions and 90% confidence intervals will be created.

Estimates for Trial Outcomes: We will estimate the mean change in hemoglobin between baseline and the 2 day nadir, the proportion of patients who have a drop in hemoglobin level of 2 g/dL or greater defined as major bleeding, as well as the mean change in INR from baseline to after the index procedure, baseline to day 1, and baseline to day 2, and the proportion of patients in whom the post transfusion INR is less than 1.5 from the observed pilot data. We will also estimate the proportion of patients who during the 2 days following randomization experience transfusion associated cardiac overload (TACO), and, as well mortality, and the mean length of hospital stay and ICU stay. TRALI is likely to be too rare to estimate rates. Estimated proportions and means and 90% confidence intervals will be created for each outcome using the data from the entire pilot trial (i.e. combining the data from the two assigned treatment arms). The change in hemoglobin level will be compared according to assigned plasma strategy using a Wilcoxon rank sum test with an alpha level of 0.05. Absolute and relative differences for continuous levels and event rates by assigned treatment will be estimated and 90% confidence intervals will be calculated to identify potential treatment differences for safety and for study planning purposes. We will use alpha of 0.01 for secondary outcomes to account for multiple comparisons. We will examine the

following subgroups: liver disease, ICU patients, INR 1.5 to 1.75 vs 1.76 to 1.99, 2.0 to 2.5 and procedure with biopsy vs no biopsy.

Characteristics of Enrolled Sample of Patients: Descriptive statistics, including means, standard deviations, medians, ranges, and frequency distributions, will be examined for all relevant measures. Transformations of measures will be considered based on distribution diagnostics and outlier analyses. The baseline characteristics of the patients in the entire trial will be described. Moreover, the characteristics of patients in the two arms of the trial will be compared using chi-square statistics for categorical variables and t-tests or Wilcoxon rank-sum statistics for continuous variables in order to identify major imbalances that may be relevant to the pilot outcome comparisons by assigned treatment. We will compare INR before and 4 hours after discontinuation of heparin.

8. Data and Safety Monitoring

An independent Data and Safety Monitoring Board (DSMB) consisting of members appointed by the Principal Investigator and approved by the National Heart, Lung, and Blood Institute (NHLBI) will monitor the study, advise the NIH Program Office and provide input to the Steering Committee. Prior to each meeting the members of the DSMB will declare any conflicts. In the event of a conflict, the remaining members will determine if conflict limits the member's ability to participate. The DSMB will include experts in transfusion, biostatistics, and ethics.

The DSMB will approve the study protocol before patient recruitment is initiated, as well as any subsequent changes to the study protocol and consent. The Principal Investigator will notify the NIH of all changes and local IRB approval will be required. The DSMB will monitor accruing data, protocol deviations, and SAEs at a formal review half way through (55 patients) study enrollment to confirm that the patients in the trial are being cared for safely.

Adverse events will be monitored in two distinct ways: the expedited reporting of deaths (within 24 hours of notification) and Serious Adverse Events (SAE) that are unexpected and related to the study protocol (within 1 week of notification)to the DSMB members and NHLBI staff, and the scheduled reporting of adverse events and study outcome event rates to DSMB members at the meeting half way through the study and at the end of the trial.

Adverse events that are study outcomes : 1) Major Bleeding. 2) Mean Change in Hemoglobin Level 3) Red blood cell transfusion 4) Transfusion Associated Cardiac Overload (TACO) i.e., congestive heart failure, and 5) Transfusion Related Acute Lung Injury (TRALI), will be systematically collected. In addition, clinical sites will submit an SAE report for all unexpected serious adverse events that are possibly associated with the study intervention and for all deaths. The DSMB chairperson/medical safety officer will review the SAE report and supporting documentation provide by the site (including local investigator assessment of relationship to the protocol) to determine whether the event is related to the study intervention and whether the event was unexpected.

The NHLBI or the DSMB chairperson may decide to convene the entire DSMB to discuss issues related to the individual event.

The DSMB will review all reported adverse events and transfusion arm at the regularly scheduled meetings.

The DSMB may advise early termination of the trial for safety reasons or make other recommendations regarding modifications to the protocol.

Each clinical site will comply with local IRB adverse event reporting.

9. Reporting Results

9.1 Individual Results

This study is performed under usual care conditions. Patient care is managed by the treating physicians who will notify subjects of medical test results, as they deem necessary. The study staff will not provide any medical results to the subjects.

9.2 Aggregate Results

The study will not notify participants of the trial results.

9.3 Professional Reporting

The results of the study will be presented at medical conferences and submitted to peer review journals for publication.

10. Bibliography

1. Wallis JP, Dzik S. Is fresh frozen plasma overtransfused in the United States? *Transfusion.* 2004;44(11):1674-1675.
2. Murad MH, Stubbs JR, Gandhi MJ, et al. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. *Transfusion.* 2010;50(6):1370-1383.
3. Whitaker BIS, K.;Schulman,J.;Green,J. The 2009 national blood collection and utilization survey report. 2011. Accessed October 14, 2011, 2011.
4. Dzik W, Rao A. Why do physicians request fresh frozen plasma? *Transfusion.* 2004;44(9):1393-1394.
5. Callum J.L D, W.H. The use of blood components prior to invasive bedside procedures: A critical appraisal. In: Minttz PD, ed. *Transfusion Therapy: Clinical Principles and Practice*. 3rd ed. Bethesda, MD: AABB Press; 2010:1-35.

6. Segal JB, Dzik WH, Transfusion Medicine/Hemostasis Clinical Trials N. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion.* 2005;45(9):1413-1425.
7. Dzik WH. Predicting hemorrhage using preoperative coagulation screening assays. *Current hematology reports.* 2004;3(5):324-330.
8. Desborough M, Stanworth S. Plasma transfusion for bedside, radiologically guided, and operating room invasive procedures. *Transfusion.* 2012;52 Suppl 1:20S-29S.
9. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion.* 2006;46(8):1279-1285.
10. Stanworth SJ, Walsh TS, Prescott RJ, et al. A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Crit Care.* 2011;15(2):R108.
11. Chowdary P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol.* 2004;125(1):69-73.
12. Triulzi DGJM, E.L. A Descriptive Analysis Of Plasma Use In The REDSIII Hospital Network. *Transfusion (in press).* 2013.
13. Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. *Transfusion.* 2010;50(6):1227-1239.
14. Patel IJ, Davidson JC, Nikolic B, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *Journal of vascular and interventional radiology : JVIR.* 2012;23(6):727-736.
15. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol.* 2004;126(1):139-152.
16. Yang L, Stanworth S, Hopewell S, Doree C, Murphy M. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. *Transfusion.* 2012;52(8):1673-1686; quiz 1673.
17. Veelo DP, Vlaar AP, Dongelmans DA, et al. Correction of subclinical coagulation disorders before percutaneous dilatational tracheotomy. *Blood transfusion = Trasfusione del sangue.* 2012;10(2):213-220.
18. Muller MC, Arbous MS, Spoelstra-de Man AM, et al. Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial. *Transfusion.* 2014.
19. Zou S, Stramer SL, Notari EP, et al. Current incidence and residual risk of hepatitis B infection among blood donors in the United States. *Transfusion.* 2009;49(8):1609-1620.
20. Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion.* 2010;50(7):1495-1504.
21. Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. *Transfusion.* 2012;52(1):160-165.
22. Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion.* 2011;51(2):338-343.

23. Popovsky MA, Audet AM, Andrzejewski C, Jr. Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. *Immunohematology.* 1996;12(2):87-89.
24. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. *J.Bone Joint Surg.Am.* 1999;81(1):2-10.
25. Toy P, Gajic O, Bacchetti P, et al. Transfusion related acute lung injury: incidence and risk factors. *Blood.* 2011.
26. Triulzi DGJM, E.L.;Fiebig, E.; Wu, Y.; Ness P.M.; Kor D.; Chowdhury D.; Fleischmann D. A Descriptive Analysis of Plasma use in the REDS-III Hospital Network. *Transfusion.* 2013;53(Supplement S2):38A.
27. Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion.* 2004;44(12):1774-1789.
28. CDC. Pneumonia (Ventilator-associated [VAP] and non-ventilator- associated Pneumonia [PNEU] Event. 2015; http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf. Accessed June 4, 2015, 2015.
29. CDC. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line associated Bloodstream Infection). 2015; http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf. Accessed June 4, 2015.
30. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.