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A Multi-disciplinary “Think Tank”: The Top 10 Clinical Trial Opportunities in Transfusion Medicine from the NHLBI Sponsored 2009 State of the Science Symposium

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Abstract

Background—In September 2009, the National, Heart, Lung, and Blood Institute (NHLBI) convened a State of the Science Symposium in Transfusion Medicine to identify phase II/III clinical trials that would provide important information to advance transfusion medicine.

Methods—Seven multidisciplinary Subcommittees developed proposals in the following areas: a) platelet product use, b) neonatal/pediatric transfusion practice, c) surgical transfusion practice, d) intensive care unit (ICU) and/or in trauma transfusion practice, e) plasma/cryoprecipitate product use, and therapeutic apheresis practice, f) red blood cell (RBC) product use/blood conservation management, and g) medical transfusion practice or blood donor studies. The committees consisted of transfusion medicine specialists, hematologists, cardiovascular surgeons, anesthesiologists, neonatologists, critical care physicians, and clinical trial methodologists. Proposals were presented and an External Panel evaluated and prioritized each concept for scientific merit, clinical importance, and feasibility.

Results—24 concepts were presented by the Subcommittees. Ten concepts addressed four areas deemed most important: 1) platelet transfusion strategies to prevent/mitigate bleeding in neonates and patients with hematologic malignancies, 2) RBC transfusion trigger strategies to improve overall outcomes in different patient populations, 3) evaluation of optimal plasma:platelet:RBC ratios in trauma resuscitation, and 4) pathogen inactivation of platelets to improve platelet transfusion safety. Conclusions: The proposal themes not only represent inquiries about the

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indications for transfusion, but also epitomize the lack of consensus when clinical practice lacks a strong evidence base. Ultimately, the purpose of this publication is to provide a “blueprint” of ideas for further development rather than endorse any one specific clinical trial design.

Keywords

clinical trials; transfusion medicine; platelets; red blood cells; trauma; pediatrics; cardiac surgery; pathogen-inactivation; intensive care

Introduction

The transfusion of blood components in the United States (U.S.) has escalated in the past 20 years; yet, indications for this rise in blood utilization are limited.¹ Patients who receive transfusion therapy are diverse and are treated by a wide range of physicians in neonatology, pediatrics, internal medicine, oncology, pulmonology, cardiology, anesthesiology, surgery, critical care, emergency medicine, hematology, and transfusion medicine. A significant gap exists between the increase in blood utilization and the evidenced-based research essential to adequately guide transfusion practices in unique patient populations and considering the multiplicity of diseases requiring supportive transfusion therapies in the U.S. The National, Heart, Lung, and Blood Institute (NHLBI) recognized the distinct merit of evidence-based transfusion practices, and in 2002 established the Transfusion Medicine and Hemostasis Clinical Trials Network (TMH CTN). The TMH network consists of seventeen clinical centers located in distinct geographic locations in the U.S., with its investigational efforts sustained by a Data Coordinating Center, New England Research Institutes (MA). The physicians who comprise the network are both pediatric and adult clinicians who specialize in hematology/oncology, hemostasis/thrombosis, and/or transfusion medicine. The primary objective of the TMH CTN is to design and execute multi-centered, pediatric and adult clinical trials that compare treatments in hemostatic disorders and evaluate both novel and existing blood product therapies. The TMH CTN is now in its eighth (of a ten) year funding cycle and has launched four studies in hemostasis [the Rituximab for the Treatment of Patients with Congenital Hemophilia and High Titer Inhibitors (RICH) study, the Heparin-Induced Thrombocytopenia/Thromboembolism Retrospective Analysis of Data on Incidence and Outcomes of Study (HIT-RADIO), the Study of Thrombotic Thrombocytopenic Purpura And Rituximab (STAR), and the Initial Treatment of Patients with Immune Thrombocytopenic Purpura (ITP²) study] and three clinical trials in transfusion medicine [the Determination of the Optimal Prophylactic Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients (PLADO) study², the Resolving Infections in Neutropenic Patients with Granulocytes (RING) clinical trial, and the REd CELL Storage Age Study (RECESS)]. In an effort to identify the next generation of clinical trials that would provide important new information to advance transfusion medicine therapies and the treatment of patients with hemostatic and thrombotic disorders, the NHLBI convened a State of the Science (SoS) Symposium. The principal goal of the SoS Symposium was to characterize the diverse areas of clinical trials research that would complement as well as *supplement* the therapeutic issues that define the various disciplines within Transfusion Medicine and Hemostasis/Thrombosis. In addition to the Transfusion Medicine Specialists and the Hemostasis/Thrombosis clinicians of the TMH network, this *enhanced* “Think Tank” was

comprised of specialists in cardiovascular surgery, anesthesiology, neonatology, critical care medicine, and clinical trial methodology. The symposium presented opportunities for investigators to define future clinical research directions of their field(s) and to interact with other investigators and constituent organizations to obtain new perspectives.

This article outlines the processes by which the SoS Transfusion Medicine (SoS:TM) contributors developed the designs and methods of the “Top Ten” phase II and III clinical trials believed to be the potential novel studies for the next 5 - 10 years that would most critically impact and significantly optimize the utilization of blood components in a sundry of supportive care measures among diverse patient populations.

Methods and Materials

The SoS Symposium was a multi-disciplinary effort designed to identify clinical research issues paramount to transfusion medicine and hemostasis/thrombosis, and that would be highly likely to inform clinical practice once evaluated in a clinical research trial. The NHLBI selected a Chair to spearhead the SoS Symposium, whose task was to collaborate with NHLBI in the selection for each of the major fields (hemostasis/thrombosis, and transfusion medicine) a Chair and Co-Chair. In transfusion medicine, the SoS:TM Oversight Committee identified seven potentially fertile clinical practice areas for research. Subcommittees were charged with developing clinical trial proposals in the following areas: a) use of platelet products, b) neonatal/pediatric transfusion practice, c) transfusion practice in surgery, d) transfusion practice in intensive care unit (ICU) and/or in trauma patients, e) use of plasma, fresh frozen plasma (FFP), cryoprecipitate products, and use of therapeutic apheresis, f) use of red blood cell (RBC) products and blood conservation management, and g) transfusion practice in medical (e.g., oncology) patients or studies of blood donors. Each Subcommittee was comprised of a Chair and co-Chair who were chosen by the SoS:TM Oversight Committee. Members of each Subcommittee were chosen by their respective Chair and co-Chair and included experts in transfusion medicine, clinical end-users, as well as at least one methodological expert (Appendix A). The seven Subcommittees convened on a regular basis (at least monthly) for eight months until the time of the SoS Symposium (September, 2009). The mandate of each Subcommittee was to identify up to five clinical trial concepts specific to their scientific area and to develop these ideas into written proposals for consideration as a phase II or III clinical trial. Each 2-3 page proposal included the following sections 1) background and rationale, 2) primary hypothesis, 3) primary endpoint, 4) secondary hypotheses, 5) secondary endpoint(s), 6) study population (inclusion/exclusion criteria), 7) clinical trial design with sample size calculations, 8) feasibility information, and 9) references. Sample size calculations for all trial proposals were estimates for the suggested trial design. However, all estimates require confirmation thus specific details have not been provided. The estimates were included in each proposal to aid the External Panel in assessing feasibility of each study being successfully performed. Twenty four proposals were completed by the seven Subcommittees and these were provided to the External Panel comprised of five experts in transfusion medicine (Appendix A). The External Panel had one month to review the proposals in preparation for the SoS Symposium. The 24 proposals (Appendix B) were presented at the symposium. An open

question and discussion format among the TM External Panel and meeting attendees/presenters followed each oral presentation.

The task of the External Panel was to provide a brief description of each proposal's strengths and weaknesses, and utilizing a grading system of 1 (being the lowest) to 5 (being the highest), evaluate and score each concept on the basis of three criteria: a) scientific merit, b) clinical importance, and c) feasibility. Scientific merit addressed the overall scientific impact the findings would have on clinical outcomes in the patient population studied. Clinical importance was a measure of the influence a study would have on altering standard practice if, once completed, the study's proposed novel intervention was demonstrated to be superior to the standard clinical practice. Finally, feasibility or the potential for a study to be successfully executed and completed was also evaluated.

The NHLBI charged the External Panel with identifying those clinical studies that could be executed through the infrastructure of a network in contrast to those trials that could be completed within the infrastructure of a single site. The External Panel was also asked to identify those clinical trials that might be of interest to the commercial sector, and vice versa, those trials that would likely only be accomplished if Federal support was provided. The External Panel met in a closed session following the Symposium presentations to categorize the twenty-four high-priority TM concepts into a high, middle, and lower tier. The remainder of this paper is an in-depth discussion of the ten clinical trial proposals that were categorized into the high tier.

Results

The top tier clinical trials represented four primary themes within the field of transfusion medicine, namely: 1) platelet transfusion strategies to prevent or mitigate bleeding in neonatal and adult patients, 2) RBC transfusion trigger strategies to improve overall outcomes in different patient populations, 3) trauma resuscitation with various plasma to platelet to RBC ratios, and 4) pathogen inactivation (PI) of platelet products to improve the safety of platelet transfusions

Platelet transfusion strategies to prevent or mitigate bleeding in neonatal and adult patients

Incidence of Moderate and Severe Bleeding in Thrombocytopenic Premature Neonates Treated with a Restrictive versus (vs) Liberal Platelet Transfusion Approach: The Neonatal Platelet Transfusion Threshold (NeoPlaTT) Study--- Presented by the SoS:TM Neonatal and Pediatric Subcommittee

Background & Rationale: Thrombocytopenia affects 20 - 35% of patients admitted to neonatal intensive care units (NICUs). The incidence is highest among the most premature infants. In at least 25% of premature infants (5 - 9% of NICU admissions in the U.S., or 20,000 - 36,000 neonates per year), one or more platelet transfusions are ordered in an attempt to decrease the risk of hemorrhage.³⁻⁶ Consensus about the platelet count vis-à-vis the benefit/risk ratio of a platelet transfusion in newborns has yet to be established. Recent publications have demonstrated great variability in the platelet transfusion thresholds

selected by neonatologists whether in North America or in Europe.^{4,5} Clinical equipoise exists as to whether a restrictive or more liberal platelet transfusion threshold is appropriate to prevent moderate to severe bleeding in neonates, and recent publications have highlighted the need for an adequately powered, randomized controlled trial to address this question and help guide best transfusion practices.^{5,6}

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of this proposed study is that a restrictive platelet transfusion approach will not be inferior to a liberal approach in the prevention of moderate to severe bleeding among thrombocytopenic preterm neonates. The primary endpoint would be the incidence of moderate and/or severe bleeding defined by the presence of intraventricular hemorrhage (IVH), intracranial hemorrhage (subdural, epidural, intraparenchymal, cerebellar), pulmonary hemorrhage, gastrointestinal hemorrhage $\pm$ necrotizing enterocolitis (NEC), genitourinary bleeding, other bleeding at surgical sites, intra-abdominal bleeding, or oozing at puncture sites that necessitate a transfusion. The secondary hypothesis is that neuro-developmental outcomes at 18 - 24 months of age would be similar among thrombocytopenic neonates treated with a restrictive rather than a liberal platelet transfusion strategy.

The proposed design is that of a randomized, multicenter, non-inferiority phase III clinical trial that compares the incidence of moderate and severe bleeding among thrombocytopenic neonates treated with a restrictive versus a liberal platelet transfusion approach.

The parents of all eligible infants admitted to participating NICUs would be approached for enrollment to the trial, within the first 48 hours of life, irrespective of the infant's platelet count. Infants whose parents or guardians agree to participate in the study would be randomized equally (1:1) to a restrictive or to a liberal arm, and would be stratified by birth weight (<1,000 grams vs 1,000 - 1,500 grams). An example of the randomization scheme might be for the liberal arm, low risk assigned, between days 1-14 would have a platelet levels for transfusion at 50,000 plts/ μ l and the same levels for 14 days old. Whereas, those patients assessed as high risk and randomized to the liberal arm would have a platelet threshold on days 1-14 of 100,000 plts/ μ l versus on 14 days old the levels would be 70,000 plts/ μ l. If randomized to the restricted arm plt levels would be for example Days 1-14 low risk at 30,000 plts/ μ l level and for those 14 days old a 20,000 plts/ μ l level versus those that are high risk at days 1-14, 60,000 level plts/ μ l and 14 days old a 50,000 plts/ μ l level. Once randomized, patients would stay in their assigned study arms throughout the duration of their NICU stay or until a post-conception age of 44 weeks is reached, whichever occurs first. Within each of these arms, platelet transfusion thresholds would be determined based on post-natal age and bleeding risk assessment ("high risk" versus "low risk"). "High risk" would be defined as a) having a diagnosis of intracranial hemorrhage or extension of bleeding within the previous 7 days, b) being coagulopathic, defined as INR > 2, PTT > 1.5 times normal for age, and/or fibrinogen <100 mg/dl within the last 48 hours, c) receiving indomethacin or Ibuprofen administration within the prior 24 hours, or receiving heparin for anticoagulation (not for line patency) or TPA; d) receiving dopamine or dobutamine at rates >5 mcg/kg/min; e) being mechanically ventilated with FiO₂ > 0.4; and/or f) prior to or within 48 hours of a surgical procedure or lumbar puncture.

Whereas each subject would remain in their originally assigned study arm throughout their entire hospital stay (or until a post-conception age of 44 weeks is reached), the subjects' platelet transfusion thresholds might change over time as the latter would be dependent on clinical condition and bleeding risk assessment (Table 1). Platelet dosing, regardless of product type, would be standardized throughout the study period per each institution. In cases of acute/major bleeding during surgery, platelet transfusions would be administered at the clinician's discretion, in deviation of the study's thresholds. The analysis would be performed using the intention-to-treat principle, regardless of additional transfusions, trial dropouts, or protocol deviations.

It is estimated that such a clinical trial would require approximately 2,252 patients. Enrollment could be completed in about 2 years if 25 centers each would recruit approximately 50 thrombocytopenic infants per year.

Randomized Controlled Trial (RCT) Comparing Prophylactic Platelet Transfusions versus (vs) Therapeutic Only Platelet Transfusions in Thrombocytopenic Patients with Hematologic Malignancies---Presented by the SoS:TM Platelet Product Subcommittee

Background & Rationale: Patients with severe thrombocytopenia are at increased risk of bleeding. In many countries, the standard approach to prevent excessive bleeding in patients undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) for a hematologic malignancy is the use of prophylactic platelet transfusions. At present, no single clinical trial has been conducted that provides evidence demonstrating whether prophylactic platelet transfusions are superior, inferior or equivalent to therapeutic transfusions in the event of bleeding.^{7,8} Several trials have investigated lowering the threshold for prophylactic transfusions, as well as examined platelet dose in this patient population. The PLADO trial investigated the latter by studying 1350 thrombocytopenic patients who were randomized to received either a low ($1.1 \times 10^{11}/m^2$), medium ($2.2 \times 10^{11}/m^2$), or high ($4.4 \times 10^{11}/m^2$) platelet doses/transfusion. Patients were transfused at a threshold of $10 \times 10^9/L$. There was no increase in bleeding risk when transfusing either low or high dose platelets compared to the standard dose.²

The need for any prophylactic platelet transfusion therapy is currently being challenged in Europe. In two separate RCTs being conducted in Germany and the United Kingdom, respectively, a prophylactic (platelets administered at a transfusion trigger of 10×10^9 platelets/L) plus therapeutic platelet transfusion strategy is being compared to a therapeutic-only transfusion strategy whereby platelets are transfused for onset of WHO grade II or greater bleeding.^{8,9} The trials are currently ongoing.

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of the proposed trial is that a platelet transfusion strategy to treat bleeding (therapeutic platelet transfusions only) is as safe as a combined therapeutic and prophylactic platelet transfusion strategy, the latter transfusions given for a morning platelet count of $10 \times 10^9/L$ in patients undergoing chemotherapy and/or HSCT as determined by clinically significant bleeding. The secondary hypothesis of the study is that the total number of

platelets transfused per patient will be less in the “therapeutic-only” arm compared to the “prophylactic/therapeutic” transfusion arm.

The trial as proposed would be a Phase III, multicenter, prospective, randomized control trial, comparing “therapeutic-only” and “prophylactic/therapeutic” platelet transfusion strategies with a primary endpoint of clinically significant bleeding. Treatment allocation would be stratified by center and diagnosis. Prospective study participants would be those with hematologic or other malignancies who are undergoing chemotherapy, immunotherapy and/or radiation therapy. These patients would be expected to have marrow aplasia, either primary (primary marrow disorder) or induced (e.g., chemotherapy) and would be anticipated to have a hypoproliferative thrombocytopenia resulting in platelet counts of $10 \times 10^9/L$ for 5 or more days. The proposed sample size for this study is estimated to be 1,800 patients; which would require approximately 20 participating sites to recruit an estimated 3 patients/month over a 3 year period.

RBC Transfusion Trigger Strategies to Improve Outcomes in Different Patient Populations

Impact of a liberal red blood cell transfusion strategy on neurologically intact survival of extremely low birthweight infants: The transfusion and brain injury (TABI) trial--Presented by the SoS:TM Neonatal and Pediatric Subcommittee

Background & Rationale: In recent decades, clinicians have conjectured on the benefits and risks of RBC transfusion in preterm newborns and have been informed by sparse randomized control trial data. Although there have been two recent medium-sized, randomized control trials,¹⁰⁻¹² clear evidence-based guidelines on the optimal hemoglobin values to target for transfusion therapy remain uncertain. The two randomized controlled trials that have been completed are the PINT trial, that includes its follow-up study, PINT-OS, and the Iowa trial.¹⁰⁻¹² The two trials significantly differed in design, study population, and hemoglobin thresholds for transfusion. Not surprisingly, the two studies arrived at differing conclusions regarding neurologic outcomes upon NICU discharge.

Both trials independently shared the common hypothesis that a higher hemoglobin transfusion threshold may confer neuroprotection in premature infants. The Iowa study demonstrated that the lower hemoglobin threshold arm led to worse outcomes of periventricular leukomalacia or grade IV intraventricular hemorrhage on head ultrasound¹². The PINT trial revealed that the cognitive sub-scale of the Bayley assessment at 18 - 24 months was significantly worse in the low threshold arm¹⁰. The on-going concern for determining hemoglobin thresholds in preterm infants has not been alleviated by these two studies and warrants a newly designed, larger RCT¹⁰⁻¹²

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of this proposed trial would be that use of a higher hemoglobin transfusion threshold for infants weighing <1000 grams at birth in order to maintain hemoglobins in the higher ranges throughout the infants' NICU stay would lead to a higher survival rate at the time of discharge as well as better neurodevelopment outcomes at age 18 - 24 months. A composite outcome of death or significant neuro-developmental impairment in survivors at age 18 - 24 months would be evaluated and neurodevelopmental status would be assessed by the

standardized Bayley instrument. A second hypothesis would be that maintaining a high hemoglobin in extremely low birth weight infants would increase survival to hospital discharge free of three severe morbidities: bronchopulmonary dysplasia, retinopathy of prematurity (stage 3 or higher), or serious brain abnormality (periventricular leukomalacia, other white matter abnormality, or significant ventriculomegaly) on cranial ultrasound at a post-gestational age of 36 weeks. Another secondary hypothesis would be that a higher hemoglobin threshold would reduce serious brain abnormalities on cranial ultrasound examination, namely grade II - IV intraventricular hemorrhage, periventricular leukomalacia, other white matter abnormality, or significant ventriculomegaly.

Infants would be eligible for enrollment if they weighed <1000 grams at birth, were 22 weeks of gestational age, and were < 29 weeks and < 48 hours old. These preterm infants would be randomized either to a low hematocrit transfusion trigger arm (38.5%) or to a higher hematocrit transfusion trigger arm (45.5%). This clinical trial would be larger than previous studies and would require randomization of 1793 subjects in order to evaluate 1614 subjects for 80% power, to detect a 7 point difference on the Bayley III Mental Developmental Index instrument. Owing to the large sample size required, the feasibility of adequate enrollment could be accomplished through partnerships with other research programs such as the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and international sites, similar to the collaborative endeavor in the PINT trial network

RBC transfusion trigger trial in critically ill pediatric patients--- Presented by the SoS:TM Neonatal and Pediatric Subcommittee

Background & Rationale: Pediatric intensive care unit (PICU) patients frequently receive RBC transfusions although the optimal pre-transfusion hemoglobin and hematocrit values to elicit administration of RBCs have not been definitively established. One large multicenter PICU randomized clinical trial, limited to patients who were in relatively good clinical condition and were administered few transfusions, compared a restrictive to a liberal pre-transfusion strategies based on different hemoglobin/hematocrit trigger values¹³. Patients were excluded if they had active bleeding at initial evaluation, hemodynamic instability, and/or cardiovascular compromise. The decision to suspend the assigned restrictive RBC transfusion threshold to some 14% of patients weakened the study's conclusion of no disadvantage to the restrictive RBC transfusion strategy¹³. Thus, an improved prospective randomized clinical trial, with less restrictive eligibility criteria would provide data to determine whether a restrictive or a liberal RBC transfusion strategy is safe and efficacious for a wider group of PICU patients.

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of this study would be that PICU patients transfused using a restrictive RBC transfusion strategy would have an outcome that is not inferior and possibly superior to PICU patients transfused using a liberal RBC transfusion strategy. The primary endpoint would be a composite outcome defined as death within 30 days of randomization, cardiac arrest within 30 days of randomization, or a longer-than-expected stay in the PICU. Secondary endpoints of the study would include: 90-day all cause mortality, number of RBC and other blood

product transfusions, and infection(s). This prospective, multi-center, randomized phase III clinical trial would require the enrollment of children < 21 years of age who are admitted to the PICU. Temporary exclusion would include those patients with active bleeding >2 mL/kg/hour. However, once bleeding diminished to < 2 mL/kg/hour for at least three hours, patients would be eligible for the study. Patients discharged from Extracorporeal Membrane Oxygen (ECMO) support would also be eligible to participate. Subjects would be randomized at the earliest point after admission to the PICU, and patients in the PICU for longer than 72 hours would no longer be eligible. Subjects would be immediately randomized to a restrictive arm (transfusion hemoglobin trigger <7g/dL) or a liberal arm (transfusion hemoglobin trigger < 10g/dL). The transfused volume of RBCs would be 5ml/kg for each one gm/dl of hemoglobin below the assigned pre-transfusion trigger value. Within 12 hours of completion of the RBC transfusion, hemoglobin and/or Hct measures would be obtained. The age of RBC units would not be a limiting factor, and any licensed storage medium would be accepted. All RBC units for study administrations would be pre-storage leukoreduced RBCs.

The estimated sample size for the study is 3136 patients which would necessitate evaluating 3484 patients in total. Based on the TRIPICU study data¹³, the feasibility of this study design is promising and would suggest that 19 sites could reach target enrollment in approximately 4 years. Establishing a partnership with the National Collaborative Pediatric Critical Care Research Network of the NICHD, which has an established infrastructure (some clinical sites and a data coordinating center) would suffice to initiate this study. Nonetheless, an additional 12 sites would have to be added in order to reach target enrollment and complete this study in four years.

Transfusion trigger trial in cardiac surgery---Presented by the SoS:TM Surgical Subcommittee

Background & Rationale: Patients undergoing cardiac surgery such as cardiopulmonary bypass frequently receive RBC transfusions in the postoperative period. An estimated 11% of RBC resources in the U.S. provide supportive therapy for patients undergoing coronary artery bypass surgery, and another 20% of blood transfusions are associated with cardiac surgery.¹⁴⁻¹⁵ The optimal hemoglobin level for transfusion in patients undergoing cardiac surgery is unknown, yet the rates of RBC transfusion vary between 10 - 70% with a mean of 4 - 5 RBC units being administered per patient. A study of RBC transfusions administered to 1915 patients with coronary artery bypass surgery patients revealed a 70% increase in 60-month mortality¹⁶, and in a perioperative RBC transfusion cohort of 10,289 coronary artery bypass surgery patients, an association between long-term survival and pre-operative anemia was determined to be an independent risk factor for death.¹⁷ To date, there has been no adequately powered randomized clinical trial, to evaluate what the optimal hemoglobin transfusion threshold should be in elective cardiac surgery patients.

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of this study would be to determine if a liberal transfusion strategy (transfusion threshold hemoglobin of 10g/dL) is associated with a lower incidence of composite outcome of all cause mortality at 30 days, recurrent myocardial infarction, infection, and other complications within 30 days of enrollment compared to a restrictive transfusion strategy

(transfusion threshold hemoglobin <7g/dL). The primary endpoint would be a composite outcome of all cause mortality at 30 days, and in-hospital complications including serious infection (pneumonia, mediastinitis/deep sternal infection, sepsis), acute renal failure, stroke, prolonged ventilation > 48 hours, and myocardial infarction. A second hypothesis for this study would be that patients randomized to the liberal transfusion strategy, when compared to the restrictive transfusion strategy, would have decreased events including the individual components of the primary outcome, short- and long-term mortality, unscheduled readmission, and multiple organ dysfunction syndrome (MODS) in the postoperative period.

This clinical trial would enroll patients 18 years and older, scheduled for elective cardiac surgery and who would be likely to receive a RBC transfusion based on a Transfusion Risk Understanding Scoring Tool (TRUST) score of 3 or more.¹⁸ Prospective patients would be consented in the preoperative period and enrolled provided they had a hemoglobin < 10g/dL. Patients would be randomly allocated to either the liberal or restrictive transfusion group. Patients randomized to the liberal transfusion strategy would receive one unit of packed RBCs following randomization and would receive throughout their hospitalization (up to 30 days) enough red cells to raise their hemoglobin above 10g/dL when their hemoglobin concentration was found to be below 10 g/dL. Patients randomized to the restrictive transfusion arm would be permitted to receive a transfusion if they developed symptoms related to anemia or if their hemoglobin concentration fell below 7g/dL. Symptoms of anemia triggering symptomatic transfusion would include: 1) definite angina requiring treatment with sublingual nitroglycerin or equivalent therapy, 2) new unexplained tachycardia or hypotension.

Measurements of troponin concentrations and ECGs would be performed every 12 hours for 1 day, then daily for 2 days, or until discharge from the hospital. Patients would be followed up at 30 days and 6 months post enrollment, or at the end of the study, to review their medical status and record any admissions to the hospital. The primary outcome is estimated to occur in 15% of patients necessitating a sample size of 4190 patients to detect a 25% relative effect.

Transfusion trigger trial in coronary artery disease---Presented by the SoS:TM Surgical Subcommittee

Background & Rationale: Patients with acute coronary syndrome and coronary artery disease frequently develop anemia secondary to iatrogenic blood loss from invasive procedures as well as from multiple antithrombotic therapy.¹⁹ Those patients with acute coronary syndrome who develop bleeding have a very high risk of death (relative risk= 5.4), recurrent myocardial infarction (relative risk= 4.4), and frequently require RBC transfusion.²⁰ Cardiologists frequently transfuse patients to maintain a hemoglobin concentration > 10g/dL to avert myocardial ischemia that may be precipitated by low hemoglobin concentrations. However, data on ICU patients suggest that the risk of myocardial infarction is greater in patients transfused for a hemoglobin of 10g/dL than in patients transfused at 7g/dL.²¹ Observational data investigating the effects of RBC transfusions are biased, and the two large trials previously mentioned¹⁸⁻¹⁹ that evaluated transfusion thresholds excluded patients with myocardial infarction. A randomized clinical trial to evaluate transfusion

thresholds in anemic patients with acute coronary syndrome has not been conducted and as a result is necessary to address this common and important clinical question.

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of this study would be to determine if a liberal transfusion strategy is associated with a lower incidence of composite outcome of all cause mortality at 30 days, recurrent myocardial infarction, emergent percutaneous intervention (angioplasty or stent insertion) or coronary artery bypass graft surgery within 30 days of enrollment when compared to a restrictive transfusion strategy.

The primary endpoint would be to determine a composite outcome of all cause mortality at 30 days, recurrent myocardial infarction, emergent percutaneous intervention (angioplasty or stent insertion) or coronary artery bypass graft surgery within 30 days of enrollment.

Patients who are 18 years or older with: 1) STEMI (ST segment elevated myocardial infarction), 2) NSTEMI (Non ST segment elevation myocardial infarction), 3) unstable angina, or 4) stable coronary artery disease, and who would undergo cardiac catheterization during their index hospitalization would be screened. To be eligible for enrollment, the patient would need to have a hemoglobin concentration $<10\text{g/dL}$ at the time of random allocation. Patients would be excluded for: 1) uncontrolled bleeding at the cardiac catheterization puncture site or needing surgical repair, 2) retroperitoneal bleeding requiring surgery, 3) clinical and/or hemodynamic instability as determined by the treating physician, and 4) anticipated cardiac surgery within the next 30 days.

Patients randomly allocated to the liberal transfusion strategy would receive one unit of packed red cells following randomization and receive enough blood to raise the hemoglobin concentration above 10g/dL any time the hemoglobin concentration fell below 10g/dL during the hospitalization, for up to 30 days. Patients randomized to the restrictive strategy would receive a transfusion if they developed symptoms related to anemia. Transfusion would also be permitted but not required in the absence of symptoms when the hemoglobin level would fall below 8g/dL . One RBC unit would be allowed and the presence of symptoms would be re-evaluated as a transfusion would be solely administered in this case to relieve symptoms. If a transfusion was given for a hemoglobin level below 8g/dL , a sufficient amount of RBCs would be administered to increase the hemoglobin concentration above 8g/dL .

Symptoms of anemia in the symptomatic arm would include: 1) definite angina requiring treatment with sublingual nitroglycerin or equivalent therapy, and 2) new unexplained tachycardia or hypotension. All standard of care tests and results (ECG, troponin, CK) would be recorded, and for the study, troponin levels (every 12 hours for 1 day, and then daily for 2 days), and daily ECGs (for 3 days) would be done. Patients would receive a follow up telephone call at 30 days and 6 months after enrollment to review their medical status and any re-hospitalizations.

The sample size required would be several thousand patients depending on the frequency of outcomes in the composite outcome. The feasibility of the study is based on the commonness of the illness, and the success of many large trials in this same population.

Of note, a pilot study for this trial is underway under the leadership of Jeffrey Carson (UMDNJ-Robert Wood Johnson Medical School). The Myocardial Infarction and Transfusion (MINT) study funded by the American Recovery & Reinvestment Act of 2009 is a phase II clinical trial aimed at randomizing 200 adults to either a liberal (transfused for a hemoglobin concentration $<10\text{g/dL}$) or restrictive (transfused for a hemoglobin concentration $<8\text{g/dL}$ or for symptoms) RBC transfusion strategy. Data collected in MINT will inform the feasibility and design of a larger phase III clinical trial (as described above).

Transfusion requirements in critical care-patients with evidence of coronary syndromes (TRICC-PECS Study)---Presented by the SoS:TM ICU/Trauma Subcommittee

Background & Rationale: The Transfusion Requirements In Critical Care (TRICC) trial suggested that hemodynamically stable ICU patients without heart disease did not benefit from RBC transfusion when their hemoglobin was $>7\text{g/dL}$.²¹ In fact, mortality was 25.9% in the liberally transfused group vs 21% in the group that was permitted to drop their hemoglobin level to 7g/dL .²¹ Patients with active heart disease were excluded from the trial. Subject with a history of ischemic heart disease who were eligible to participate appeared to do worse in an underpowered subgroup analysis ($n=357$).²¹ Other retrospective data also suggest that patients with a history of heart disease would benefit from a higher hemoglobin threshold, perhaps as high as 11g/dL . The main question in this proposed trial would be: Does transfusion of RBCs to improve hemodynamic stability in ICU patients with ischemic heart disease and a hemoglobin level $>10\text{g/dL}$ improve patient outcomes?

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis in this study would be that adult ICU patients with a history of ischemic heart disease, secondary to either past coronary artery disease or old myocardial infarction, would benefit from having their hemoglobin level maintained above 10g/dL . The primary endpoint would be the change in Multiple Organ Dysfunction (MODS) score (with death counted as the highest MODS score). The secondary hypothesis is that the benefits of early RBC transfusion will be most obvious at 7 days.

The study would be designed as a multicenter, randomized clinical trial following the model of the TRICC trial²¹; yet, it would only include patients with a history of ischemic heart disease. Thus, hemodynamically stable patients in the ICU, with a history of ischemic heart disease would be eligible; once their hemoglobin approached 10g/dL they would be randomized to either a lower hemoglobin transfusion trigger arm (trigger of 8g/dL) or a higher hemoglobin transfusion trigger arm (trigger of 10g/dL). Ideally, mortality would be most informative as the primary endpoint. However, this endpoint would require a sample size of 30,000 patients rendering this size trial unrealistic. Thus, the change in MODS score was selected as the primary endpoint with death counted as the highest MODS score. The trial as proposed with 90% power would require a sample size of 628 patients per arm. The enrollment of 1256 patients would necessitate recruitment from a minimum of 40 sites, and would extend beyond 3 years.

Trauma resuscitation with various plasma to platelet to RBC ratios

Prospective Randomized Optimum Plasma to Platelet Ratios (PROPPR Study)---Presented by the SoS:TM ICU/Trauma Subcommittee

Background & Rationale: Several studies have documented that a diversification in blood product allocation contributes to potentially preventable hemorrhagic deaths. Despite these findings, many physicians continue to follow the Advanced Trauma Life Support (ATLS) guidelines, and begin fluid resuscitation with crystalloids, followed by RBCs. Typically this practice continues without administering plasma, platelets, or more rarely, cryoprecipitate *until* many liters of crystalloids and RBCs have been administered. The practice of massive transfusion resuscitation with more than 10 units of RBCs is based on little clinical evidence. Multiple studies have suggested on the one hand, that this standard resuscitation strategy exacerbates the initial coagulopathy of trauma, thereby increasing the risk of mortality, and on the other hand, that survival is improved with the increased use of more equal plasma-to-platelet-to-RBC ratios. Reviews done by surgeons and blood bank experts of massive transfusion practices suggesting a benefit from early and increased use of plasma/platelets along with RBCs early in the resuscitation require further study.

Borgman et al., recently described improved survival with increased fresh frozen plasma (FFP)-to-RBC ratios in combat casualties.²² Perkins and colleagues also described improved survival with increased platelets-to-RBC ratios in combat casualties.²³ In a recent retrospective analysis of blood component ratios used in civilian trauma, massive transfusion practices were found to vary widely among trauma centers, and survival was associated with increased plasma/platelet-to- RBC ratios (meaning the transfusion of more plasma and platelets than usual).²⁴ Several other civilian institutions have reviewed and analyzed similar retrospective data. The 16 center retrospective study by Holcomb et al.,²⁴ is the largest civilian trauma transfusion study to date and has revealed that an increase use of plasma/platelets was strongly associated with improved survival rates. Similarly, the work of Maegele and colleagues in Europe documented similar findings, namely in truncal hemorrhage situations.²⁵ Currently, the Department of Defense in the U.S. is funding the prospective observational multi-center massive transfusion trauma (PROMMTT) study coordinated by the University of Texas Health Science Center at Houston (UTHSCH). This 10 center study is set to enroll >300 massively transfused trauma patients in 12 months, and will describe component utilization and outcomes of these trauma patients. The PROPPR randomized clinical trial proposes to evaluate increased plasma and platelet ratios in massively transfused trauma patients with the primary objective of improving clinical outcomes. The data gathered in the PROMMTT study will inform the design of the PROPPR study.

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis would be that transfusion of high ratios of plasma/platelets-to-RBC rather than transfusion of the standard of care component ratios will increase survival of trauma patients with truncal bleeding who are massively transfused. The primary endpoint would be the between-group differences in mortality at 6 hrs, 24 hrs, 48 hrs, and 30 days. Secondary hypotheses would include that transfusion of high ratios of plasma/platelet-to-RBC would reduce both complications, and the length of hospitalization.

The PROPPR study is proposed as a randomized, multicenter trial. Community consultation, eliciting feedback, criticism, and suggestions from the community, would be critical for this type of study design.²⁶ The target study population is major trauma patients, > 16 years of age, who may require massive transfusions. Patients would be randomized to either a high ratio platelet/plasma-to-RBC (1:1:1) arm or to a low platelet/plasma-to-RBC ratio group (1:1:2) arm. Eligible patients would have received at least one RBC unit in the Emergency Department. Patients predicted to receive a massive transfusion would be ascertained by means of an algorithm developed from the retrospective study data, and validated with the ongoing prospective PROMMTT study data. Approximately 27 Level I trauma centers that span the continental U.S. and international centers have expressed interest in participating. Interest has been expressed by nine centers from the Resuscitation Outcomes Consortium (ROC), eight sites from the NIH-funded Glue Grant program, fifteen NIH CTSAs, and all ten sites that participated in the PROMMTT trial. The PROPPR trial is intended as a 3.5 year study, with the first 18 months dedicated to finalizing study design, IRB submission/approval, and training at each of the clinical sites. The study is projected to enroll 580 massive transfusion patients, and would necessitate screening approximately 3000 patients who receive at least 1 RBC unit in the Emergency Department at approximately 12 sites.

Pathogen inactivation (PI) of platelet products to improve the safety of platelet transfusions

Evaluation of pathogen-reduced platelets---Presented by the SoS:TM Platelet Product Subcommittee

Background & Rationale: Bacterial contamination of platelet products and subsequent transmission of the bacteria with platelet transfusions remains a major cause of morbidity and mortality in thrombocytopenic patients, partially due to associated leucopenia and immunosuppression. Although standard culture testing exists for the detection of bacteria in platelet products, this surveillance technique is not typically applied to all platelet products. Moreover, it has now been demonstrated that available bacterial detection strategies (culturing at 24 hours) will not detect low levels of bacteria which can result in clinical sepsis after transfusion of a stored platelet product.²⁷ An alternative approach to preventing bacterial transfusion transmission is the use of pathogen reduction technologies (PRT). One such process of pathogen reduction uses UV light in the presence of riboflavin (Mirasol), that prevents nucleic acid replication, and has been demonstrated to inactivate 3 - 6 logs of both Gram positive and Gram negative bacteria.²⁸

Preliminary studies evaluating PRT have demonstrated a decrease in the recovery and survival of autologous five-day-stored apheresis platelets treated with PRT compared to five-day-stored conventional platelets.²⁹ Radio-labeled PRT-treated platelets compared to radio-labeled conventional platelets showed recoveries of $50 \pm 19\%$ vs. $67 \pm 13\%$ and survivals of 4.3 ± 1.1 days vs. 5.9 ± 1.1 days, respectively ($p < 0.05$ for both recoveries and survivals).²⁹ However, in limited clinical trials in Europe, the PRT-treated platelets have demonstrated hemostasis and adequate post-transfusion platelet responses.

As ideal as it may seem to design a clinical trial to evaluate the prevention of bacterial transmission from platelet transfusions, such a trial is not feasible given the large sample

size required to detect such low risk bacterial transmission. Therefore, this proposed trial is designed to compare PRT platelets to standard platelets in order to evaluate if adequate hemostasis and a good safety profile can be obtained.

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis of this study would be that both Mirasol pathogen-treated apheresis platelets and pre-storage pooled platelet concentrates would be equally efficacious as standard apheresis platelets or post-storage pooled platelet concentrates (control platelets) in maintaining hemostasis in patients with hypoproliferative thrombocytopenia. The primary endpoint would be the percent of thrombocytopenic patients who experience WHO bleeding scale Grade II or greater bleeding. The study would test whether grade II bleeding or higher is non-inferior in patients who receive PRT-treated platelets and patients who receive control platelets. Two secondary hypotheses would be that post-transfusion platelet responses of patients receiving PRT-treated platelets would not be substantially less than that observed with control platelets, and that the incidence of platelet alloimmunization would be decreased in recipients of PRT-treated compared to control platelets.

The study is proposed as a prospective, blinded, Phase III randomized clinical trial, comparing the use of PRT platelets to the use of conventional platelet transfusions in patients who develop hypoproliferative thrombocytopenia. In this population, the platelet counts would be expected to be $10 \times 10^9/L$ during five or more hospital days. The treatment allocation would be stratified for underlying disease and trial site. Patients would be randomly assigned to receive PRT-treated or standard platelet products. The platelet dose would be low dose platelets (1.1×10^{11} platelets/transfusion/ m^2) in order to ensure the hemostatic efficacy of low dose PRT-treated platelets.² Administration of RBC transfusions and γ -irradiation of blood products would be based on local practice. Physicians would be able to deviate from the transfusion trigger or platelet dose criteria for onset of bleeding or for planned surgical interventions. Trained research staff would perform daily hemostatic assessments by means of patient interview, physical exam, and chart review.

Assuming the incidence of Grade 2 or higher bleeding will be what was observed in the PLADO Trial (70%)², the target sample size would be 150 patients per arm. In order to complete the study within 8-12 months, ten trial sites, with 15 participating hospitals, would be required to enroll ~ 40 patients/month based on the enrollment data from the PLADO trial.²

Prevention of alloimmunization via pathogen inactivation of platelets--- Presented by the SoS:TM Medical and Blood Donor Subcommittee

Background & Rationale: Some patients who receive prolonged platelet transfusion support experience a significant decrease in platelet count increments despite lacking evidence of HLA sensitization detected by standard serologic methods.³⁰⁻³¹ One hypothesis for this observation is a non-immune condition that causes vascular endothelial damage demanding frequent platelet transfusions in order to stabilize and maintain vascular integrity.³² Alternatively, another theory stems from observations made in the TRAP trial and in studies of PRT platelet products in which patients who received UV irradiated platelets

either as a method to decrease alloimmunization (TRAP) or to inactivate pathogens did not experience the same degree of decay in platelet transfusion increments or inter-transfusion intervals as patients who received untreated platelets.³⁰ These outcomes raised the possibility that undetected alloimmunization to either HLA or other antigens on platelets may be responsible.. The ability of UV light treatment to inactivate antigen presenting cells and lymphocytes in platelet concentrates is supportive of this hypothesis.³³

Hypothesis, Clinical Trial Design, Sample Size, and Feasibility: The primary hypothesis is that the declining responsiveness to successive platelet transfusions seen in heavily transfused patients is due to previously undetected HLA (or other antigen) alloimmunization and that treatment with UV based PRT procedures can decrease this alloimmunization by inactivating residual WBC in the platelet products.

The primary endpoint would be a comparison of trends of the mean sequential one hour post platelet transfusion *increments* for the first 20 platelet transfusions received by each patient transfused with PI apheresis platelets vs. standard leukoreduced single donor apheresis platelets. A secondary endpoint would be the development of alloimmunization to standard leukoreduced platelet products Vs PI platelets documented by the presence of reactivity in recently available highly sensitive HLA antibody detection assays (e.g., Flow Panel Reactive Antibodies, Luminex Panel Reactive Antibodies). An additional secondary endpoint would be a comparison of the rates of platelet specific antibody reactivity that develop in both arms of the study.

This study would be designed as a multicenter, Phase III, randomized control trial, with two arms comparing patients receiving PRT- treated platelets to patients receiving standard leukoreduced apheresis single donor platelets. Adult and pediatric patients, receiving myeloablative chemotherapy/H SCT treatment for hematologic/oncologic diseases, who require extensive supportive platelet therapy would be eligible. Study participants would be enrolled and randomized prior to their first platelet transfusion, and would be followed for the first 20 – 25 transfusions, or for 8 weeks. Baseline demographic and laboratory data to be collected would include: age, gender, ethnic origin, race, height, weight, diagnosis, procedure/chemotherapy (type and date of transplant), history of prior pregnancy or transfusion, ABO type, coagulation studies (PT, PTT, Fibrinogen) CBC, platelet count, HLA/platelet specific antibody screen using a sensitive method. Daily or periodic measurements would include: platelet count, hematocrit/hemoglobin , PT/INR, PTT and fibrinogen, assessment for bleeding done every two weeks, and at the end of the study, an HLA/platelet specific antibody screen using a sensitive method.

With each platelet transfusion, a pre- and post- transfusion platelet count (at 1 hour and 18-24 hours), a platelet count of the transfused product, assessment for symptoms/signs of a transfusion reaction, recording of PaO₂, and (in the event ALI is suspected) a chest x-ray would be performed. If platelet refractoriness was suspected, HLA antibody and platelet antibody screening would be done.

The proposed study is feasible given that other large scale platelet transfusion trials (TRAP, SPRINT, and PLADO) have been successfully conducted, and is suggestive of the ease of

recruiting adequate subjects from a comparable study population.^{2,30,34} The facility of this study's conduct is further supported by more widely available, sensitive methods of HLA and platelet antibody detection. Approximately 300 subjects would need to be enrolled in total.

Discussion

The SoS symposium in transfusion medicine was a multi-disciplinary endeavor that outlined twenty-four prospective clinical research trials that, if executed over the next 5 - 10 years, could considerably advance practice in TM.³⁵ These concepts were all considered as high priority by experts in the field and carefully selected from many other potential ideas by the seven subcommittees. These twenty-four high priority proposals were carefully reviewed and scrutinized by the External Panel which selected ten concepts as the top tier studies. The scientific diversity found in this top tier of studies underscores the necessity for evidence-based research to inform and propel the discipline of transfusion medicine into the future.

Several fundamental questions are posed in the top tier protocols. What thresholds in medical and/or surgical settings should dictate the transfusion of RBCs and platelets in children and adults? From a hemostasis perspective that seeks to minimize infection and alloimmunization, which platelet products should be transfused to enhance the safety for recipients of platelet transfusions? For trauma patients, what ratio of blood components would constitute the most effective transfusion strategy to recapitulate the essence of whole blood? These exemplary questions not only typify the daily clinical inquiries about the indications for transfusions but also epitomize the lack of consensus that results when clinical practice lacks a strong evidence base. These proposals also focus on patient populations who receive most of the blood components collected in the U.S.

The concepts were developed by transfusion medicine specialists, clinical trials methodologists, and end-user physicians. The input from end-user physicians in the development of these concepts was key as none of these studies could be conducted without a solid understanding of the patient population under study, and the relevant clinical setting. The willingness of end-user clinicians to enroll their patients in a clinical trial is an invaluable measure of its feasibility and clinicians' input in the development and design stages of studies conducted in transfusion medicine is critical to their success. The purpose of this publication is to present a "blueprint" of ideas for further development, rather than to endorse a specific study design. However, it is hoped that investigators will pursue some of these high priority areas and conduct the next generation of clinical trials necessary to advance the field of transfusion medicine, and most importantly, *inform* clinical practice in a wide variety of medical and surgical settings.

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Appendix A

STATE-OF-THE-SCIENCE SYMPOSIUM ORGANIZATIONAL STRUCTURE

Chair: Morris A. Blajchman

DBDR Director, NHLBI: Keith Hoots

Branch Chief, Transfusion Medicine and Cellular Therapies, NHLBI: Simone A. Glynn

Cassandra Josephson

Steven H. Kleinman

Traci Heath Mondoro

George Nemo

There were 7 Transfusion Medicine Sub-Committees as follows:

Subcommittee 1: Platelet Product Issues

Sherrill Slichter, (Chair), University of Washington, Puget Sound Blood Center

Nancy Heddle, (Co-Chair), McMaster University

Terry Gersheimer, University of Washington, Puget Sound Blood Center

Richard Kaufman, Harvard University

Evelyn Lockhart, Duke University

Mike Murphy, University of Oxford, National Blood Service and Oxford Radcliffe Hospitals

Marty Tallman, Weill Cornell Medical College J

Dan Weisdorf, University of Minnesota

Subcommittee 2: Neonatal and Pediatric Issues

Cassandra Josephson, (Chair) Emory University, Children's Healthcare of Atlanta

Steve Sloan (Co-Chair), Harvard University, Children's Hospital of Boston

Hareesh Kirpalani, University of Pennsylvania, Children's Hospital of Philadelphia

Martha Sola-Visner, Harvard University, Children's Hospital of Boston

Ron Strauss, University of Iowa

Jack Widness, University of Iowa

Christof Dome, Institute for Social Medicine, Epidemiology and Health Economics, Charité
– Universitätsmedizin Berlin, Germany

Subcommittee 3: Surgical Issues

Jeffrey L. Carson, (Chair), UMDNJ-Robert Wood Johnson Medical School

Darryl Triulzi, (Co-Chair), University of Pittsburgh

John Marshall, St. Michaels Hospital, University of Toronto

Lena M. Napolitano, University of Michigan

Chris Stowell, Harvard University

Richard Weiskopf, University of California, San Francisco

Subcommittee 4 : ICU and Trauma Issues

John Hess, (Chair), University of Maryland

John Holcomb, (Co-Chair), University of Texas Health Sciences Center

Susan Assman, New England Research Institute

Howard Corwin, Dartmouth-Hitchcock Medical Center, NH

Ognjen Gajic, University of Maryland

David Hoyt, University of Maryland

Giora Natzer, University of Maryland

Michael Terrin, University of Maryland

Subcommittee 5: Plasma, FFP and Therapeutic Apheresis Issues

Ziggy Szczepiorkowski, (Chair), Dartmouth-Hitchcock Medical Center, NH

Lynne Uhl, (Co-Chair), Harvard University

Jeannie Callum, Sunnybrook Health Sciences Center, Canada

Larry Dumont, Dartmouth-Hitchcock Medical Center, NH

Sunny Dzik, Harvard University

Alan Tinmouth, University of Ottawa Center for Transfusion

Sarah Vesely, University of Oklahoma

Jeffrey Winters, Mayo Clinic, MN

Subcommittee 6: RBC, Blood Conservation and Blood Management Issues

Jonathan Waters, (Chair), University of Pittsburgh

Victor Ferraris, (Co-Chair), University of Kentucky

Elliott Bennett-Gurrero, Duke University

Art Bracey, Walter Reed Medical Center, Washington, D.C.

Aryeh Shander, Englewood Hospital and Medical Center, NJ

Maria Steiner, University of Minnesota

Stephen Vamvakas, Cedar-Sinai, CA

Subcommittee 7: Medical and Blood Donor Issues

Jeffrey McCullough, (Chair), American Red Cross

John Adamson, (Co-Chair), University of California San Diego Medical Center

Richard Benjamin, American Red Cross

Chris France, University of Ohio

Jan McFarland, University of Wisconsin, Blood Center of Wisconsin

Ed Snyder, Yale University

EXTERNAL PANEL FOR TRANSFUSION MEDICINE

Harvey Klein, (Chair), National Institutes of Health

Chris Hillyer, New York Blood Center

Naomi Luban, Children's National Medical Center, Washington DC

Paul Ness, The Johns Hopkins University

Pearl Toy, University of California, San Francisco

Appendix B

Proposed Studies for the State of the Science Symposium in Transfusion Medicine

TM-101 - Randomized controlled trial comparing prophylactic platelet transfusions (given at a platelet count trigger of $10 \times 10^9/L$) versus 'therapeutic only' platelet transfusions in thrombocytopenic patients with hematological malignancies.

TM-102 - Evaluation of pathogen-reduced platelets.

TM-103 - RBC transfusion trigger trial in critically ill pediatric patients.

TM-104 - Incidence of moderate and severe bleeding in thrombocytopenic premature neonates treated with a restrictive vs. liberal platelet transfusion approach: The neonatal platelet transfusion threshold (NeoPlaTT) study.

TM-105 - Impact of a liberal red blood cell transfusion strategy on neurologically-intact survival of extremely-low-birth-weight infants: The transfusion and brain injury (TABI) trial.

TM-106 - The use of Fresh Frozen Plasma to Prevent Bleeding in Patients Undergoing Radiographic and Bedside Procedures

TM-107 - The Use of Fresh Frozen Plasma to Preventing Bleeding in Patients Undergoing Surgical Procedures in the Operating Room

TM-108 - Transfusion Trigger Trial in Cardiac Surgery

TM-109 - Transfusion Trigger Trial in Coronary Artery Disease

TM-108 - Transfusion trigger trial in cardiac surgery.

TM-109 - Transfusion trigger trial in coronary artery disease.

TM-110 - Transfusion requirements in critical care-patients with evidence of coronary syndromes (TRICC-PECS).

TM 111 - Moderate Traumatic Brain Injury Coagulopathy Treatment Trial (Mod-TBI-CTT)

TM-112 - Prospective Randomized Optimum Platelet and Plasma Ratios, (PROPPR).

TM-113 - Plasma in Critical Care: A Sequentially Stratified, Non-Inferiority Trial of Plasma versus No Treatment for Critical Care Patients Undergoing Invasive Bedside Procedures

TM-114 - A Prospective, Randomized, Controlled Clinical Trial of Cryoprecipitate Transfusion in Cardiac Surgery Patients Experiencing Major Hemorrhage after High-Risk Cardiac Surgery

TM-115 - Phase II, Multicenter, Randomized Trial of Plasma Exchange in Severe Sepsis with Multiple Organ Failure

TM-116 - A Prospective RCT of Extracorporeal Photopheresis (ECP) for Treatment of Chronic Graft-Versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplant

TM-117 - Blood Salvage and Cancer Surgery

TM-118 - P2Y12 Inhibitors and Post-CABG Bleeding

TM-119 - Study of Safety and Efficacy of Acute Normovolemic Hemodilution (ANH) in Reducing Surgical Transfusion Rates

TM-120 - Prevention of Alloimmunization via Pathogen Inactivation of Platelets

TM-121 - Effect of the Use of Erythropoietic Stimulating Agents (ESAs), with or without Parenteral Iron, on the Transfusion Requirements in Anemic Cancer Patients Receiving Platinum-based Chemotherapy

TM-122 - Trial of Reduced-Volume Whole-Blood Collections to Mitigate the Risk of Vasovagal Reactions in Young Donors

TM-123 - Enhancing Recruitment and Retention of Novice High School Blood Donors

TM-124 - Use of Thrombopoiesis-Stimulating Agents (PSA) to Decrease Blood Product Transfusions in Patients with Liver Disease

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