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Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: Experience from the Pragmatic Randomized Optimal Platelets and Plasma Ratios (PROPPR) Trial

Deborah J. Novak¹, Yu Bai², Rhonda K. Cooke³, Marisa B. Marques⁴, Magali J. Fontaine³, Jerome L. Gottschall⁵, Patricia M. Carey⁶, Richard M. Scanlan⁷, Eberhard W. Fiebig⁸, Ira A. Shulman⁹, Janice M. Nelson⁹, Sherri Flax¹⁰, Veda Duncan¹⁰, Jennifer A. Daniel-Johnson¹¹, Jeannie L. Callum¹², John B. Holcomb¹³, Erin E. Fox¹³, Sarah Baraniuk¹⁴, Barbara C. Tilley¹⁴, Martin A. Schreiber¹⁵, Kenji Inaba¹⁶, Sandro Rizoli¹⁷, Jeanette M. Podbielski¹³, Bryan A. Cotton¹³, John R. Hess¹¹, and on behalf of the PROPPR Study Group

¹Department of Pathology, College of Medicine, University of Arizona ²Department of Pathology and Laboratory Medicine, Medical School, University of Texas Health Science Center at Houston ³Department of Pathology, School of Medicine, University of Maryland ⁴Division of Laboratory Medicine, Department of Pathology, School of Medicine, University of Alabama at Birmingham ⁵Department of Pathology and Laboratory Medicine, Medical College of Wisconsin ⁶Department of Pathology and Laboratory Medicine, College of Medicine, University of Cincinnati ⁷Division of Laboratory Medicine, Department of Pathology, Oregon Health and Science University ⁸Department of Laboratory Medicine, University of California, San Francisco ⁹Department of Pathology, Keck School of Medicine, University of Southern California ¹⁰Clinical Laboratories, Regional Medical Center ¹¹Department of Laboratory Medicine, University of Washington ¹²Sunnybrook Health Sciences Centre ¹³Center for Translational Injury Research, Division of Acute Care Surgery, Department of Surgery, Medical School, University of Texas Health Science Center at Houston ¹⁴Division of Biostatistics, School of Public Health, University of Texas Health Science Center at Houston ¹⁵Division of Trauma, Critical Care and Acute Care Surgery, School of Medicine, Oregon Health and Science University ¹⁶Division of Trauma and Critical Care, University of Southern California ¹⁷Trauma and Acute Care Surgery, St Michael's Hospital, University of Toronto

Corresponding author: Deborah J. Novak, MD, Medical Director, Blood Bank, University of Arizona Medical Center, 1501 N Campbell Avenue, Tucson, AZ 85724, TEL: 520-626-3820, PGR: 520-694-6000, FAX: 520-626-7329, djnovak28@gmail.com.

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Author Contributions:

Study concept and design: DJN, JRH

Development of local blood bank policies and procedures: DJN, YB, RKC, MBM, MJF, JLG, PMC, RMS, EWF, IAS, JMN, SF, VD, JAD-J, JC, JRH

Audited local blood use: DJN, YB, RKC, MBM, MJF, JLG, PMC, RMS, EWF, IAS, JMN, SF, VD, JAD-J, JC, JRH

Analysis and interpretation of data: DJN, JRH, JBH, EEF, SB, BCT, MAS, KI, SR, JP, BAC

Drafting of the manuscript: DJN, JRH, YB, RKC, MBM, MJF, JLG, PMC, RMS, EWF, IAS, JMN, SF, VD, JAD-J, JC

Critical revision of the manuscript for important intellectual content: DJN, JRH, JRH, JBH, EEF, SB, BCT, MAS, KI, SR, JP, BAC, YB, RKC, MBM, MJF, JLG, PMC, RMS, EWF, IAS, JMN, SF, VD, JAD-J, JC

Abstract

Background—The Pragmatic Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial was a randomized clinical trial comparing survival after transfusion of 2 different blood component ratios for emergency resuscitation of traumatic massive hemorrhage. Transfusion services supporting the study were expected to provide thawed plasma, platelets and red blood cells within 10 minutes of request.

Study Design and Methods—At the 12 Level 1 trauma centers participating in PROPPR, blood components transfused and delivery times were tabulated, with a focus on universal donor (UD) plasma management. The adequacy of site plans was assessed by comparing the bedside blood availability times to study goals and the new American College of Surgeons (ACS) guidelines.

Results—Eleven of 12 sites were able to consistently deliver 6 units of thawed UD plasma to their trauma receiving unit within 10 minutes, and 12 units in 20 minutes. Three sites used blood group A plasma instead of AB for massive transfusion without complications. Approximately 4700 units of plasma were given to the 680 patients enrolled in the trial. No site experienced shortages of AB plasma that limited enrollment. Two of 12 sites reported wastage of thawed AB plasma approaching 25% of AB plasma prepared.

Conclusion—Delivering UD plasma to massively hemorrhaging patients was accomplished consistently, rapidly and without excessive wastage in high-volume trauma centers. The ACS Trauma Quality Improvement Program guidelines for massive transfusion protocol UD plasma availability are practicable in large academic trauma centers. Use of group A plasma in trauma resuscitation needs further study.

Keywords

blood center operations; injury; massive bleeding; transfusion; shock; transfusion service operations; fresh frozen plasma (FFP); hemotherapy

INTRODUCTION

Injury is the leading cause of the loss of young adult lives, leading to 65% of all deaths among those aged 15–24 years.¹ Uncontrolled hemorrhage is the most important preventable cause of such deaths among those who sustain traumatic injury.² In these patients, rapid blood component replacement as part of treatment has been associated with improved survival and reduced total blood usage in retrospective studies.³

Since the 1970s, trauma resuscitation in North America has been conducted largely according to the American College of Surgeons Advanced Trauma Life Support (ATLS) course, giving crystalloid fluids to support intravascular volume and red blood cells (RBCs) to maintain oxygen transport while plasma and platelets were only given when indicated by laboratory measures.⁴ This empiric protocol worked for the majority of moderately and severely injured patients and was compatible with the logistics of most transfusion services where plasma was stored frozen, thawed only after an ABO blood type was available, and required half an hour to thaw and issue. However, profoundly injured soldiers and civilian

patients receiving massive transfusions appeared to benefit when plasma and RBCs were given together early and throughout the course of resuscitation.⁵⁻⁷

The Pragmatic Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial attempted to confirm the benefits of rapid, balanced blood product resuscitation in a partially-blinded, prospective, randomized comparison of resuscitation with units of plasma, platelets, and RBCs in either 1:1:1 or 1:1:2 ratios.⁸ The medical directors of the transfusion services at the participating high-volume academic trauma centers noted that the trial was potentially limited by the low number of units of blood group AB universal donor (UD) plasma available from blood suppliers. Additionally, there was concern that there would be excessive wastage if plasma was routinely thawed in advance. However, use of a thawed plasma program has previously been shown to improve delivery time and decrease waste.⁹ This paper describes the efforts of the transfusion services supporting the participating PROPPR trauma centers and the results they achieved in supplying thawed plasma in a timely manner. With the American College of Surgeons now recommending the immediate availability of thawed plasma for balanced resuscitation as a guideline and future accreditation standard, this manuscript will describe the transfusion services' experiences during PROPPR.¹⁰

METHODS

The PROPPR trial was carried out by the University of Texas Health Science Center at Houston (UTHealth) in conjunction with the Resuscitation Outcomes Consortium (ROC) and funding from the US National Heart Lung and Blood Institute (NHLBI), the US Army, the Canadian Institutes of Health Research, and Defence Research and Development Canada.¹¹ The protocol was approved by a Data Safety Monitoring Board, the US Army Human Research Protection Office, the US Secretary of the Army, Health Canada, and the Institutional Review Boards/ Research Ethics Boards of the twelve participating institutions. Because of the requirement to initiate therapy immediately on admission, the study used Exception from Informed Consent (EFIC), which required delayed consent after community consultation, and was conducted in the US under an Investigational New Drug waiver from the US Food and Drug Administration (FDA).

The 12 PROPPR trial sites were chosen in a formal selection process based on patient volume, geographic location, ability to conduct protocol-driven research, and the ability to deliver blood components in a timely manner.¹² Specifically, the sites committed to developing systems to deliver six units of UD RBCs and up to six units of UD thawed plasma and platelets to the bedside within ten minutes of patient arrival and to continue blood product support at this rate using UD or type-compatible products as long as clinically indicated. No constraints were placed on how this blood support was to be performed. To assist sites, investigators from UTHealth visited each site and walked through their processes, similar to a quality improvement approach. The final process was reviewed and approved by UTHealth investigators before sites were allowed to enroll patients.

Data on the time of patient admission, transfusion service notification of need for blood products, arrival of the first and subsequent containers of blood at the bedside, times of

individual product administration, and protocol deviations were obtained by direct observation. Data regarding the choice of primary UD plasma product as either AB or A thawed plasma, the exact plan of how many units were maintained pre-thawed, the method of thawing, and any problems with inventory over the course of the trial were acquired from the individual transfusion services.

RESULTS

Eleven of the 12 sites developed methods to successfully deliver 6 units of thawed UD plasma to the bedside in less than 10 minutes. Only one site, enrolling only two patients a month, had a higher median time of 15 minutes. The median time from patient admission to transfusion service call was 9 minutes and from transfusion service call to product at bedside was 8 minutes (Figure 1).

Three sites used blood group A plasma as UD thawed plasma. One site used group A low-titer B, obtained from male donors, to reduce the potential risk of hemolysis from anti-B infused into Group B or Group AB patients and to avoid the added risk of transfusion-related acute lung injury (TRALI). Another site used untitered group A because they did not believe that they could meet the inventory demands for pre-thawed AB plasma. The third site used group A plasma at times when inventory of group AB plasma was insufficient. A total of 141 units were transfused to AB and B patients at these 3 sites without evidence of hemolysis or other reactions. Ninety-seven of those units were not titered for anti-B. No transfusion reactions occurred. No site had to close enrollment because of a temporary lack of AB plasma and no cases of TRALI were observed in the trial.

Each transfusion service handled the problem of delivering the required blood products in its own way. As the changes in transfusion service procedures all required planning, implementation, and validation, brief descriptions are provided below. The sites are identified by the names of the city of the participating institutions. A total of approximately 4700 units of plasma were given to the 680 patients enrolled in the trial.

Baltimore

The University of Maryland Medical Center (UMMC) transfuses 37,000 units of RBCs and 24,000 units of plasma each year, or about 65 units/day.¹³ This means that 325 units of plasma would be thawed and transfused within the typical 5-day shelf-life with 6% of all plasma units given as AB units. Because the facility thaws and uses 19–20 units of AB plasma every 5 days, the decision was made to keep 15–18 units thawed at all times. AB plasma wastage initially averaged 5%. The trauma receiving unit is 250 yards from the transfusion service, so RBCs and plasma for the next randomization were pre-packaged, sealed, and placed in a monitored blood refrigerator in the unit. The package was checked every 12 hours. Plasma units were rotated back to the blood bank inventory on the fifth day of their shelf life. Fifty-two of 222 AB plasma units issued for the initial cooler and rotated back to the blood bank were outdated and wasted. It was concluded that a shorter rotation from the trauma refrigerator to the blood bank on day 4 instead of day 5 may decrease wastage.

Birmingham

The University of Alabama at Birmingham (UAB) Hospital transfuses 12,000–13,000 units of plasma each year. UAB has been transfusing five-day thawed plasma since 2006 and has maintained a supply of tagged blood products for massive transfusion protocol requests. For PROPPR, there was one cooler for each randomization group and an apheresis platelet unit always available in a satellite laboratory adjacent to the operating room and seven floors above the ED, accessible by trauma-designated elevators. All coolers were dispensed by transfusion service personnel to a trauma team courier. The plasma expiration dates were monitored twice daily. Plasma within two days of expiration was rotated. No plasma units designated for PROPPR were wasted. If AB plasma inventory was noted to be low while preparing the cooler for storage, group A plasma was substituted. Five group B and two group AB patients received from one to nine units of group A plasma for a total of 31.

Cincinnati

The Hoxworth Blood Center at the University of Cincinnati Medical Center (UCMC) uses 5-day thawed plasma. The initial PROPPR cooler contained AB plasma. Twelve thawed units each of Type A and Type O plasma were available for requests for second and third coolers, whenever the blood type was known. Eight thawed units of Type B plasma and 6 of Type AB were available for additional cooler requests. If simultaneous, multiple urgent requests occurred, the additional units were available for use. Type O patients received mixed plasma types determined by unit outdates. There were 33 units of plasma wasted due to the PROPPR study, and 3 (9%) of these units were type AB.

Houston

The blood bank at the Memorial Hermann Hospital-Texas Medical Center (MHH-TMC) is located one floor above the ED. Although there are two pneumatic tube stations inside the ED, designated runners are used to transport blood products and ensure product issue is carried out appropriately for all ED orders.¹⁴ It takes 6–8 minutes to travel between the ED and the blood bank. MHH-TMC increased the trauma inventory, especially Type AB plasma thawed for the PROPPR study, and rotated thawed AB plasma back into the general inventory at day 3. When a case was initiated, the blood bank was notified. The blood bank prepared blood products immediately with the required ratio. The average time for delivery of the first cooler was 9 minutes during PROPPR.

In order to increase the number of universal plasma units available and reduce wastage, Type AB liquid plasma (never-frozen plasma with a 26-day expiration date), was included in the regular inventory. Plasma usage was closely monitored. During the study period, 5,460 units of plasma were released for trauma massive transfusion protocol and/or PROPPR cases. The total plasma wastage was 105 units or 1.9%. Forty-one units were wasted during management of trauma cases (9 units Type AB) and 64 units wasted due to inventory management (15 units Type AB). During the study period, total AB plasma wastage was 24 units or 0.4%.

Los Angeles

At LAC+USC Medical Center, male-donor, group A plasma tested for the anti-B titer was used as the UD plasma for the PROPPR study for the purpose of maintaining TRALI mitigation efforts. Initially, a 1:50 dilution taken to antihuman globulin testing against reagent B red cells was used to determine whether a unit was “low titer.” Approximately 2 months into the study the testing was modified to use a 1:25 dilution by immediate spin to make this determination. Negative units were referred to as “low-titer A plasma” and tagged as “LT.” There was no wastage, as units were labeled as Thawed Plasma with a 5-day expiration immediately upon thawing. The units were rotated into the general thawed inventory on day 4. Of the 56 patients enrolled, 7 group B and 5 group AB patients received 1–6 units of group A plasma. Three of the group B and two of the group AB patients received 6 units of group A plasma. Post-transfusion direct antiglobulin testing performed on 4 of the AB and 4 of the B patients was negative. No adverse events were reported in AB or B patients receiving units tested by either titer method. There was a total of 44 units of group A plasma transfused to B or AB patients.

Memphis

The transfusion service at the Regional Medical Center (The MED) has two emergency refrigerators, each stocked with 10 O positive, 2 O negative RBC units and 2 AB thawed plasma. Maintaining AB thawed plasma inventory was historically challenging, so Type A plasma was used as UD plasma. Anti-B titers were not performed. Of the 42 patients enrolled, 11 (26%) received incompatible plasma with no titer performed and no adverse effects from transfusion. The MED gave 66 units of Type A thawed plasma to 3 AB and 8 B patients. The thawed plasma inventory was increased from 4 O and A plasma units to 6. Type B remained at 2. A shelf labeled PROPPR contained 6 type A thawed plasma units, 6 O positive RBC units and 6 O negative RBC units pre-labeled for the study. The blood bank at the MED constantly monitored the plasma expiration dates, with plasma wastage estimated at < 1%.

Milwaukee

The Blood Center of Wisconsin at Froedtert Hospital increased production of AB plasma in order to meet PROPPR study requirements. The Transfusion Service (TS) increased the amount of thawed plasma available for emergency release and kept 6 type AB thawed plasmas specifically for the PROPPR protocol. The TS also kept 4 type AB thawed plasmas as general stock for emergency release per normal procedure and was therefore able to consistently supply the first cooler within 10 minutes. A second cooler was started by using the rest of the thawed plasma available and/or thawing additional units. Dedicated study runners were hired to ensure coolers got to the patient bedside within the required time frame. Runners were available 24/7 and continued to transport all coolers for the duration of the massive transfusion support. Product wastage increased by having more thawed AB plasma available. Prior to PROPPR, 3–5% of thawed plasma was wasted annually. During the PROPPR enrollment period, 6% (266 units) of thawed plasma was outdated or wasted. Approximately 61% of wasted thawed plasma was type AB.

Portland

Prior to PROPPR, the transfusion service at the Oregon Health and Science University Hospital was located in a separate building and required 15 minutes to prepare and transport blood to the trauma receiving area in the ED. During PROPPR, 6 units of thawed plasma were made available by the transfusion service. To overcome transport delays, physicians ordered blood immediately upon patient arrival and a dedicated transport team was created to deliver blood to the patient. Late in the course of the study, the transfusion service was moved closer to the ED to expedite blood delivery. However, because blood was ordered before study eligibility was determined, only 31 patients received blood among 547 activations. During the 15-month enrollment period of PROPPR, average wastage per month was 7.1% compared with 4.2% per month for the 12 months prior to PROPPR.

San Francisco

In order to meet expectations for rapid release and transport of blood components to the patients in PROPPR, the Transfusion Service at San Francisco General Hospital set up the following conditions and workflow: six O positive and six O negative red cell units, six units AB plasma and one apheresis platelet unit maintained pre-labeled in the Blood Bank at all times. Upon PROPPR study activation, the Blood Bank was called and provided with patient identification. Blood Bank staff randomized the patient according to the study arm. Pre-labeled group O red cells (O positive for male patients, O negative for female patients), AB plasma and an apheresis platelet unit were labeled with unit tags completed with patient information. One copy of each of the triplicate tags was retained in the Blood Bank. Coolers were transported by dedicated study personnel who were dispatched to the Blood Bank for pickup of study coolers at enrollment. There was no change in plasma wastage rates compared to prior to the PROPPR study.

Seattle

Harborview Medical Center (HMC) had historically received all its transfusion service support from a regional blood center located 5 blocks away. As this proved inadequate for modern trauma treatment, a new transfusion service was built on site to specifically support prompt patient care and clinical trials. This service initially kept 6, and later 12 units, of AB plasma thawed at all times. Plasma and RBCs were taken to the patient in a portable blood bank refrigerator and issued at the bedside. The process was labor intensive, but supported a changing blood use culture of responsibility at HMC. Altogether, 25 of 1837 units (1.3%) of thawed AB plasma units were not administered over the 13 months that HMC was active in the trial.

Toronto

The process at Sunnybrook Health Sciences Centre included O positive and O negative red cell units pre-labeled as “Trauma, O positive” and “Trauma, O negative.” The numbers were adjusted to meet the needs of the study: 12 of each group to ensure 2 coolers could be provided as soon as possible. This process was extended to include AB thawed plasma for the PROPPR study. The applicable number of AB plasma (3 or 6 units dependent on the next treatment arm) were thawed and labeled ready to go at all times. For the first 2 months

of the study, if the AB plasma was 5 days from thaw date, a new “set” of AB plasma would be thawed, cooled, and ready just prior to the current set expiring. However, the blood bank experienced high wastage of AB plasma with the process as described. Subsequently, it was decided that on day 3 of the thawed plasma’s life, a new set of plasma would be thawed and cooled. This would allow approximately 2 days to use the older thawed AB plasma for a non-PROPPR study patient. Wastage was not eliminated as plasma use outside of a massive bleed is uncommon at Sunnybrook. In the year prior to initiation of the PROPPR study, 94% of all plasma was transfused after preparation, and 93% of prepared AB plasma. During the approximately 14 months of the PROPPR study, 87% of all plasma was transfused after preparation, and 76% of AB plasma.

Tucson

The University of Arizona Medical Center stocked 4 units of Type A, 4 units of type O, and 2 units of type B thawed plasma for immediate use. Thawed A, O, and B plasma units were maintained in accordance with the goal of avoiding transfusion with AB plasma units to non-AB patients as much as possible. Six units of Type AB plasma were stocked when the next randomization required 6 units, and 3 units when the next randomization required 3 units. Inventory management of type AB plasma determined that short-dated units were used for type AB patients and for urgent requests due to concern for TRALI risk. There were no problems meeting type AB plasma inventory needs.

The result of the AB inventory policy was a striking change in plasma wastage. Plasma wastage averaged less than 1.0% prior to the initiation of a massive transfusion protocol in 2010. A small thawed plasma inventory was added, and plasma wastage increased steadily to 7.4% by the end of 2012. Thawed plasma inventory had been increased approximately two months prior to study initiation in November 2012. Plasma wastage for 2013 was 9.5%. Using data obtained from eleven of the thirteen months of the study, AB plasma accounted for approximately 57% of wasted plasma. Post-PROPPR, a decision was made to decrease stock of Type AB thawed plasma to 4 units.

DISCUSSION

Recent experience suggests that balanced transfusion of severely injured patients with uncontrolled hemorrhage can save lives, reduce complications, and decrease total blood product use.¹⁵ The PROPPR trial was a prospective and randomized test of that hypothesis. However, for the test to be valid, the transfusion services of the participating trauma centers had to be able to provide all products in a timely manner irrespective of the group to which the patient was randomized. If it took longer to prepare plasma for the group allocated to receive more plasma, then the benefits of receiving any plasma may be lost in the wait while the higher dose was prepared.¹⁶ This situation can introduce survivor bias even within a randomized trial.¹⁷

In this study, 11 of the 12 centers met the goal of delivering the initial UD products 10 minutes after they were ordered. The twelfth center had a median of 15 minutes. Surgeons in the twelfth center attempted to compensate for this slower response time by ordering blood immediately on patient arrival. In another center where the randomized transfusion pack was

pre-positioned in the ED, the surgeons took longer (mean=15 minutes) to call for products, but received them essentially immediately. The average time from patient arrival to product at bedside was the same at both centers, but unnecessary blood bank activations were minimized at the center where packs were pre-positioned.

The data suggest that an overall increase in plasma wastage occurs with initiation of an inventory of thawed plasma for immediate use. However, the quantity of the attributable wastage varies with decisions regarding plasma management and the intensity of attention to the prevention of wastage. One-third of sites reported no appreciable increase in waste. An optimal quantity for inventory will vary according to the facility's baseline plasma use, and how unused thawed plasma is rotated back into the inventory.

The data also suggests that group A low-titer B plasma can be used as universal donor plasma in the early phases of trauma resuscitation.^{18–20} A total of 141 units were transfused to AB and B patients at the three sites without evidence of hemolysis or other reactions. Ninety-seven of those units were not titered for anti-B. No transfusion reactions occurred. This experience is valuable, but needs further exploration.²¹ Using male group A low-titer B plasma for trauma resuscitations would reduce the demand for AB plasma, take advantage of the increased safety of male-only plasma, and free AB plasma for critical uses.

Supply limitations of UD blood products are a constant concern. The importance of expanding supplies of these products was recognized early in the development of damage control resuscitation.²² Experience suggests that large hospitals can manage emergency UD plasma availability with appropriate attention to thawed inventory. Expanding thawed UD plasma availability to smaller, less busy trauma centers is important because half of all trauma patients are initially seen outside of Level 1 trauma centers. The use of liquid (never frozen) plasma is appearing, as more hospitals provide plasma early in trauma resuscitation. The shelf life of liquid plasma is up to 26 days, with reported acceptable hemostatic function.

The American College of Surgeons Trauma Quality Improvement Project issued guidelines for trauma resuscitation in November 2013, recommending that “Universal donor products should be immediately available on patient arrival to support ratio-based transfusion,” and “If MTP triggers are met, transfuse universal plasma and RBC in a ratio between 1:1 and 1:2.”¹⁰ The new guidelines represent a major shift in the paradigm of trauma resuscitation and blood product provision that has existed for more than a generation. These recommendations are outside the capabilities of many facilities now, but are likely to become accreditation requirements in the near future. Maintaining a 5-day thawed plasma inventory, utilizing blood type A low-titer anti-B plasma for emergency resuscitation, and rapid-thaw systems can all help make plasma more widely and quickly available.

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Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Study Group

Clinical Coordinating Center: John B. Holcomb, MD; Charles E. Wade, PhD; Deborah J. del Junco, PhD; Erin E. Fox, PhD; Nena Matijevic, PhD (Laboratory Committee co-Chair); Jeanette Podbielski, RN; Angela M. Beeler, BS.

Data Coordinating Center: Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Joshua Nixon, MS; Roann Seay, MS; Savitri N. Appana, MS; Hui Yang, MS; Michael O. Gonzalez, MS.

Core Laboratory: Lisa Baer, MS; Yao-Wei Willa Wang, MD; Brittany S. Hula, MS; Elena Espino, BS; An Nguyen, BS; Nicholas Pawelczyk, BS; Kisha D. Arora-Nuttall, BS; Rishika Sharma, MD; Jessica C. Cardenas, PhD; Elaheh Rahbar, PhD; Tyrone Burnett, Jr., BS; David Clark, BS.

Resuscitation Outcomes Consortium: Gerald van Belle, PhD; Susanne May, PhD; Brian Leroux, PhD; David Hoyt, MD; Judy Powell, BSN, RN; Kellie Sheehan, BSN.

Systems Biology Committee: Alan Hubbard, PhD (co-Chair); Adam P. Arkin, PhD.

Transfusion Committee: John R. Hess, MD, MPH (co-Chair); Jeannie L. Callum, MD (co-Chair)

PROPPR Clinical Sites (listed in order of number of patients enrolled):

University of Texas Health Science Center at Houston: Bryan A. Cotton, MD, MPH; Laura Vincent, BSN, RN, CCRP; Timothy Welch; Tiffany Poole, DC; Evan G. Pivalizza, MD; Sam D. Gumbert, MD; Yu Bai, MD, PhD; James J. McCarthy, MD; Amy Noland, MD; Rhonda Hobbs, MT(ASCP)SBB.

University of Washington: Eileen M. Bulger, MD; Patricia Klotz, RN; Lindsay Cattin, BA; Keir J. Warner, BS; Angela Wilson, BA; David Boman, BA; Nathan White, MD, MS; Andreas Grabinsky, MD; Jennifer A. Daniel-Johnson, MBBS.

University of California, San Francisco: Mitchell Jay Cohen, MD (Systems Biology and Laboratory Committees co-Chair); Rachael A. Callcut, MD, MSPH; Mary Nelson, RN, MPA; Brittney Redick, BA; Amanda Conroy, BA; Marc P. Steurer, MD, DESA; Preston C. Maxim, MD; Eberhard Fiebig, MD; Joanne Moore; Eireen Mallari, MT.

University of Cincinnati: Peter Muskat, MD; Jay A. Johannigman, MD; Bryce R. H. Robinson, MD; Richard D. Branson, MSc, RRT; Dina Gomaa, BS, RRT; Christopher Barczak, BS, MT(ASCP); Suzanne Bennett, MD; Patricia M. Carey, MD; Christopher N. Miller, MD; Helen Hancock, BS, MT(ASCP); Carolina Rodriguez, BA.

University of Southern California: Kenji Inaba, MD; Jay G. Zhu, MD; Monica D. Wong, MS; Michael Menchine, MD, MPH; Kelly Katzberg, MD, FACEP; Sean O. Henderson, MD; Rodney McKeever, MD; Ira A. Shulman, MD; Janice M. Nelson, MD; Christopher W. Tuma, BA, MT(ASCP), SBB; Cheryl Y. Matsushita, BS, MT(ASCP).

Shock, Trauma and Anesthesiology Research - Organized Research Center (STAR-ORC), R Adams Cowley Shock Trauma Center, University of Maryland Medical Center: Thomas M. Scalea, MD; Deborah M. Stein, MD, MPH; Cynthia K. Shaffer, MS, MBA; Christine Wade, BA; Anthony V. Herrera, MS; Seeta Kallam, MBBS; Sarah E. Wade, BS; Samuel M. Galvagno, Jr, DO, PhD; Magali J. Fontaine, MD, PhD; Janice M. Hunt, BS, MT(ASCP) SBB; Rhonda K. Cooke, MD.

University of Tennessee Health Science Center, Memphis: Timothy C. Fabian, MD; Jordan A. Weinberg, MD; Martin A. Croce, MD; Suzanne Wilson, RN; Stephanie Panzer-Baggett, RN; Lynda Waddle-Smith, BSN; Sherri Flax, MD.

Medical College of Wisconsin: Karen J. Brasel, MD, MPH; Pamela Walsh, AS, CCRC; David Milia, MD; Allia Nelson, BS, BA; Olga Kaslow, MD, PhD; Tom P. Aufderheide, MD, MS; Jerome L. Gottschall, MD; Erica Carpenter, MLS(ASCP).

University of Arizona: Terence O'Keeffe, MBChB, MSPH; Laurel L. Rokowski, RN, BSN, MKT; Kurt R. Denninghoff, MD; Daniel T. Redford, MD; Deborah J. Novak, MD; Susan Knoll, MS, MT(ASCP) SBB.

University of Alabama at Birmingham: Jeffrey D. Kerby, MD, PhD; Jean-Francois Pittet, MD (Anesthesia Chair); Patrick L. Bosarge, MD; Carolyn R. Williams, RN, BSN, BSME; Shannon W. Stephens, EMTP; Henry E. Wang, MD, MS; Marisa B. Marques, MD.

Oregon Health and Science University: Martin A. Schreiber, MD; Jennifer M. Watters, MD; Samantha J. Underwood, MS; Tahnee Groat, MPH; Craig Newgard, MD, MPH; Matthias Merkel, MD, PhD; Richard M. Scanlan, MD; Beth Miller, MT(ASCP)SBB.

Sunnybrook Health Science Center: Sandro Rizoli, MD, PhD; Homer Tien, MD; Barto Nascimento, MD, MSc, CTBS; Sandy Trpcic; Skeeta Sobrian-Couroux, RN, CCRP, BHA; Marciano Reis; Adic Pérez, MD; Susan E. Belo, MD, PhD; Lisa Merkley, BA, MLT, CBTS; Connie Colavecchia, BSc, MLT.

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Figure 1. Blood bank process times (in minutes)

Times from trauma patient admission to transfusion service call, call to product delivery, and product delivery to breaking of the randomization seal on the package averaged 9, 8, and 5 minutes. Variation across centers appears to be based on differences in both medical practice patterns and transfusion service procedures.