PROTOCOL:

Prehospital **R**esuscitation **O**n **H**elicopter **S**tudy (PROHS)

IRB NUMBER: HSC-GEN-14-0735
IRB APPROVAL DATE: 09/23/2014

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2. Study Sites

10 Level I Adult Trauma Centers

- 4-5 with blood products on helicopters
- 4-5 with only crystalloid on helicopters

3. Overview:

The Prehospital Resuscitation On Helicopter Study (PROHS) is a pragmatic, multicenter, prospective observational study of air ambulance-based prehospital resuscitation regimens currently utilized at the participating sites. Patients will be enrolled at participating sites that currently have blood products available on air ambulances and other sites that do not. This study will not change the current prehospital standard of care for resuscitation. The primary outcome will be in-hospital mortality and the primary unit of analysis will be the patient. Other outcomes of interest will include time to hemostasis, hospital length-of-stay, number of ventilator-free and ICU-free days, incidence of major surgical procedures, complications (transfusion-related acute lung injury [TRALI], acute kidney injury [AKI], multiple organ failure [MOF], acute respiratory distress syndrome [ARDS], sepsis, intra-abdominal complications, thromboembolic complications, compartment syndromes), lifesaving interventions, the amount and type of blood products and concentrates transfused (including prehospital), wastage of prehospital blood products and concentrates, use of external and internal hemostatic devices, and functional status at discharge/discharge destination.

4. Hypothesis and Specific Aims:

The objective of this study is to compare the effectiveness of two different existing prehospital resuscitation approaches in severely injured trauma patients transported by air ambulance in a pragmatic, multicenter, prospective observational study. Hypothesis: Patients with severe traumatic injuries who are evacuated to a Level I trauma center on air ambulances and who receive plasma and/or red blood cells (RBCs) (Group 1) will have lower in-hospital mortality compared to patients evacuated on an air ambulance and who don't receive any prehospital blood products (Group 2).

Aim 1.1 Compare routinely collected prehospital vital signs and demographics, prior to in-transit resuscitation to assess whether groups were similar at baseline.
Aim 1.2 Compare in-hospital mortality and time to death between groups, adjusting for potential confounders including center.
Aim 1.3 Assess additional outcomes of interest, including amount of products infused and subsequent need for early hospital transfusion.

5. Background:

Injury is the leading cause of death in adults and children between the ages of 1 and 44 years. The staggering numbers of years of productive life lost due to hundreds of thousands of deaths annually from injuries (over 180,000 in the U.S. in 2007) demands more urgent attention be made to this major public health problem.[1-5] Approximately 40% of in-hospital deaths among injured patients involve massive truncal hemorrhage that is considered potentially salvageable.[6-12] Multiple retrospective military and civilian studies have reported that blood component ratios (*i.e.*, plasma: RBC) approaching 1:1 are associated with significant decreases in 24-hour and 30-day mortality among injured patients.[13-21] Based on these results, many centers have placed thawed or liquid plasma in the ED, allowing earlier infusion of blood products and avoiding delayed achievement of a balanced transfusion.[22] Moving even earlier, recent prehospital studies from the military and the Mayo Clinic have shown that *prehospital* plasma and RBCs is not only feasible, but associated with improved coagulation status on arrival and subsequent outcomes.[23-25]

Observational studies are critically important mechanisms to guide future interventional studies. Accordingly, we have completed a prospective observational study of in-hospital blood product use at ten trauma centers (PRospective Observational Multicenter Major Trauma Transfusion study, PROMMTT).[26] PROMMTT data was then used in the planning of a recently completed twelve site in-hospital Phase III randomized clinical trial to evaluate the effectiveness and safety of the 1:1:1 (platelet: plasma: RBC) versus 1:1:2 (Pragmatic Randomized Optimal Plasma and Platelet Ratio, PROPPR, trial). Additionally, we have recently demonstrated that hospital-wide implementation of damage control resuscitation (DCR) translates into earlier use of plasma, platelets and RBCs as the primary resuscitative fluids for bleeding trauma patients in our ED, operating room (OR) and intensive care unit (ICU) settings.[27] These efforts were associated with a significant decrease in crystalloid use, improved metabolic status, decrease in MOF and improved 24-hour and 30-day survival.[22, 27]

In addition to a potential benefit from balanced resuscitation, timing plays a significant role in projected outcomes of severely injured patients. Moore et al., revealed that the majority of massive transfusion patients traditionally receive ≥ 10 units of blood in the first 6 hours after injury and have the highest incidence of death during the same time frame.[18] Likewise, civilian data from Los Angeles County document that early death is largely from hemorrhage and occurs early after admission, while late death is uncommon.[6] Furthermore, we have shown that placing plasma and RBCs in the ED decreased blood use and improved outcomes,[22, 28] suggesting that similar results may occur by placing the same products prehospital. The DoD has placed prehospital plasma on air ambulances and with ground units, and associated improved outcomes with this change. Zielinski has recently shown that prehospital plasma and RBC transfusions are feasible in the civilian prehospital arena and are associated with improved coagulation status at ED arrival.[24]

Thawed AB plasma (TP), with a shelf life of 5 days, is the product most widely used to achieve early approximation of a balanced ratio. TP, along with O negative RBCs, was placed on all Memorial Hermann Hospital (MHH) Life Flight air ambulances in September 2011 as the primary resuscitative fluid for patients suffering hemorrhagic shock. In addition to routinely collecting acid/base and coagulation data (including thrombelastography [TEGs]) on arrival in all 1369 severely injured, Level I patients (our highest level of trauma activations, patient numbers from the 2010 MHH Trauma Registry), we have adopted the DoD transfusion hemorrhage control approach, including the use of tourniquets and hemostatic dressings in the prehospital and ED settings, making our center an excellent location for this type of study.

Prehospital resuscitation practices in the US differ significantly in approach, with systems either using crystalloids or some combination of plasma, RBCs. Use of artificial colloids or blood product concentrates is much less common. To date, no large systematic studies have evaluated the use of prehospital plasma and RBCs in severely injured patients compared to crystalloids. Thus we propose a pragmatic, multicenter observational study to compare two different prehospital resuscitation approaches. Because most preventable hemorrhagic deaths occur within minutes to a few hours of injury, it is critical to evaluate both short- and long-term outcomes following blood product transfusions. The proposed study design and appropriate analyses focusing on both short and long-term outcomes will 1) minimize the survival bias that plagues previous studies,

2) provide a more complete picture of the effectiveness of prehospital plasma and RBC transfusion vs. the previous standard, crystalloid-based resuscitation, and 3) provide realistic effect sizes that could be used to design a future multicenter clinical trials.

5.1. Preliminary Data

By making plasma immediately available for release to trauma patients upon arrival to the operating room, Cotton et al., demonstrated a reduction in both mortality and blood product utilization.[13] Prior to implementation in February 2006, the authors' institution did not have thawed AB plasma available for immediate release and did not have a protocol in place for its rapid and sustained delivery. In light of the success of their efforts, the authors increased the immediately available thawed AB plasma from four to six units in their trauma operating room.[27]

Building on this study, a 2009 internal audit by investigators at MHH demonstrated that, despite having a massive transfusion protocol in place, time to first plasma transfusion was significantly delayed. At that time, saline solutions and universal donor O negative RBCs were available in the ED, while TP and platelets were kept exclusively in the Blood Bank. In collaboration with Transfusion Medicine colleagues, we placed four units of TP in the ED refrigerator along with the existing four units of RBCs to expedite delivery and transfusion of plasma. After implementation of the TP protocol in February 2010, we noted a significant reduction in time to hanging the first unit of plasma among all Level I patients (83 minutes to 42 minutes) and also in those who would ultimately receive a massive transfusion (59 minutes to 19 minutes).[22, 29] What is more clinically relevant is that *time from requesting* TP to transfusion of the first unit of plasma was reduced from 30-40 minutes to two minutes or less. Consistent with our hypothesis, moving TP to the ED/trauma bay was associated with significant reductions in 24-hour transfusion of RBC, plasma, cryoprecipitate and platelets and a significant decrease in massive transfusion rates at our facility (from 39% vs. 27%). Most importantly, after controlling for anatomic (injury severity score [ISS]), physiologic (weighted-revised trauma score [RTS]) and metabolic injury (base deficit), logistic regression identified TP in the ED as an independent predictor of increased 30-day survival (OR 1.6, 95% C.I. 0.194-0.956, p=0.038).[22, 27]

Beginning in January 2009, our Trauma faculty began to work closely with MHH's aero-medical program (Life Flight, LF) to champion the adoption and consistent implementation of permissive hypotension and limited crystalloid-based resuscitation (the other two components of DCR). The previously validated ABC Score[30] was used to determine if prehospital transfusion was needed. We recently completed a study comparing prehospital Focused Assessment with Sonography for Trauma (FAST) exam (an ABC Score component) to the ultrasound exams performed by ED physicians.[31] This demonstrated that prehospital flight personnel are trained and competent in performing FAST exams. At the same time, resuscitations were discussed at Morning Report (sign-out) among the Trauma and Surgical Critical Care faculty, fellows, and residents. Non-compliance and "outliers" were identified in real-time fashion and feedback was provided to all involved parties (prehospital, ED, OR, Trauma, and Surgical Critical Care personnel).

As previously mentioned, earlier use of plasma and RBCs has been associated with improved survival in trauma patients with substantial hemorrhage, and accordingly we have recently completed a single center retrospective study of plasma and/or RBC prehospital resuscitation on air ambulances.[32] We hypothesized that prehospital transfusion of thawed plasma and/or RBCs would result in improved patient coagulation status on admission and survival. Adult trauma patient records were abstracted to obtain patient demographics, shock, coagulopathy, outcomes and blood product utilization between September 2011 and April 2013. Patients arrived by either ground or two different air ambulance companies. All patients transfused blood products (either pre or in-hospital) were included in the study. One air ambulance system (LF) had thawed plasma and RBCs while the other air (OA) and ground transport systems used only crystalloid resuscitation. Patients receiving prehospital transfusions were compared with all other patients meeting entry criteria to the study cohort. All comparisons were adjusted in multi-level regression models. There were 8536 adult trauma patients admitted during the 20-month study period, of which 1677 met inclusion criteria. They represented the most severely injured patients (ISS = 24 and mortality = 26%). There were 792 patients transported by ground, 716 by LF and 169 on OA. Of the LF patients, 137 (19%) received prehospital transfusion. There were 942 units (244 RBCs and 698 plasma)

placed on LF air ambulances, with 1.9% wastage. Prehospital transfusion was associated with improved acid base status on hospital admission, decreased use of blood products over 24 hours, a reduction in the risk of death in the sickest patients over the first 6 hours after admission and negligible blood product wastage. In this small single center pilot study, there were no significant differences in 24-hour (odds ratio 0.57, p=0.117) or 30-day in hospital mortality (odds ratio 0.71, p=0.441) between LF and OA. In conclusion, prehospital plasma and RBC transfusion were associated with improved early outcomes, negligible blood product wastage, but not an overall survival advantage. One limitation to this single-site study was the inability to completely adjust for injury severity because the patients who received prehospital blood were consistently the most seriously injured. This indication bias can be minimized in a multisite study where some sites do not have prehospital blood available and therefore similar severely injured patients who did not receive blood will be available to compare to patients receiving prehospital blood. Similar to the data published from the ongoing war, improved early outcomes are associated with placing blood products prehospital, allowing earlier infusion of lifesaving products to critically injured patients.[23, 25]

6. Research Design:

This is a pragmatic, observational, multi-center clinical observational study that will observe and evaluate the effectiveness of two different prehospital (air ambulance only) resuscitation regimens for severely injured trauma patients. The two groups are 1) plasma and/or RBCs, and 2) no plasma or RBCs.

6.1. Study Population:

The target population for this study is trauma patients who are transported to one of the participating Level I trauma centers via air ambulance, directly from the scene, and meet the eligibility criteria listed below.

6.2. Setting:

Level I adult trauma centers will participate in this study. Approximately eight to ten centers will be selected based on their current prehospital resuscitation procedures aboard their air ambulances and other factors including annual number of patients transported. Currently, some Level 1 trauma centers have blood products available on their air ambulances, while others do not. It is not the intent of this study to change current prehospital practice at the participating centers, but to leverage the differences that already exist. For this reason, some sites will be chosen that currently have blood products available on air ambulances and some will be chosen that do not. Sites will be chosen so that the number of patients transported by air ambulance per year will be similar in the sites that have blood products and the sites that do not. However, the primary unit of analysis is the patient, not the site. Therefore, the primary analysis will examine mortality in patients who received blood prehospital compared to those who did not, adjusted for center. Air ambulances must be staffed at a minimum with EMT-Ps and nurses with the capability to transfuse blood products, and sites will be objectively balanced based on their patient volumes, outcomes, geographical distribution and the ability to submit standardized data to TQIP. The participating sites must agree to not change their prehospital resuscitation regimens during the enrollment phase of the study. No other trauma care variable will be controlled. Furthermore, to minimize the confounding variables of transport time and level of available prehospital care and to contribute relevant data to the military system, this study will be performed on air ambulance transports only.

6.3. Inclusion Criteria (At-risk population):

Patients meeting the following inclusion criteria will be enrolled in this study.

1) Patients with traumatic injuries received directly from the scene via air ambulance service (did not receive a lifesaving intervention at an outside hospital or healthcare facility)
2) Estimated age of 15 or older or greater than/equal to a weight of 50 kg, if age unknown

6.3.1. Subset Inclusion Criteria (Highest risk population):

Patients meeting the following inclusion criteria will be followed for direct observation data collection after hospital admission.

1) Meet at least one of the following during prehospital care: HR >120 bpm, SBP ≤90 mmHg, penetrating truncal injury, tourniquet application, pelvic binder application or intubation.
2) Received blood products during transport (for those facilities with blood product availability)

6.4. Exclusion Criteria:

1) Prisoners, defined as those received directly from a correctional facility. Justification: Prisoners are excluded because of their vulnerable population status.

6.5. Study Design Rationale:

Observational studies of the comparative effectiveness of prehospital trauma resuscitation interventions face significant challenges. These issues are outlined in a paper stemming from our experience in PROMMTT.[33] In a relatively austere environment such as prehospital transport, accurate ascertainment of the extent and severity of the patient's injury and bleeding can suffer because of the minimal diagnostic tools available as well as the sensitivity and specificity of those tools. Another major challenge is the availability and accuracy of data reflecting the indications that led to the prehospital intervention and on the timing and intensity of the interventions provided. Recording valid trauma data often is subordinated by the competing urgency of administering resuscitation interventions fast enough to prevent injury-related disability or death.

To address these challenges and optimize limited resources, the proposed pragmatic prospective prehospital study will collect detailed, directly observed data at the bedside of a defined subset of highest-risk patients. Additionally, internal validity and generalizability will be improved by obtaining existing, and therefore low-cost, trauma registry data on the entire population of at-risk (i.e., helicopter-transported) trauma patients.

The inclusion criteria for the highest risk subgroup to be followed by direct observation include four variables examined in our single center observational study.[32] In that study, it was noted that 15% of patients who received blood during air transport did not meet at least one of the following four criteria (SBP < 90 mmHg, HR > 120 bpm, penetrating torso injury, or intubation). This represents the false negative rate for these criteria (1-sensitivity). Additionally, 54% of patients who did not receive blood during air transport met at least one of these four criteria (false positive rate, or 1-specificity). To minimize the number of missed highest risk patients using only these four criteria, we will add tourniquet application and pelvic binder application to the list of inclusion criteria as well as receiving a prehospital transfusion. If patients met one of the 6 criteria, but did not receive a prehospital transfusion, we will ask the transporting helicopter medics/nurses why a transfusion was not initiated.

7. Study Procedures:

7.1. Screening:

Clinical research staff will be continuously available on a 24/7 basis at each participating center to conduct screening and collect data on those patients who were transported via the air ambulance service and meet the inclusion/exclusion criteria. Research staff must be present in the ED when the patient arrives and ascertain eligibility and other information directly with the air ambulance medical crew. Direct patient observation and data collection will begin immediately upon the patient's arrival to the ED for those patients who meet the highest risk inclusion criteria and will continue until 1) the patient expires, or 2) hemostasis and initial resuscitation including blood products has been achieved. Specific guidelines for direct observation will be outlined in the manual of operations (MOO). Since this is an observational study, no study interventions, drugs,

new laboratory data or devices will be randomized or assigned and all patient care will follow the participating site's policies and procedures.

7.2. Study Data Collection Process:

Data will be collected from sites' existing trauma registries on all subjects meeting the inclusion criteria for at risk patients. These data include outcomes and complications through the subjects' initial hospital day or day 30, whichever comes first. Registry data will include patient demographics and injury characteristics, prehospital and admission vital signs, death/discharge, incidence of major surgical procedures, complications, lifesaving interventions (both pre-hospital and in hospital), total transfusions, and injury severity score (ISS). Complications to be included are TRALI, AKI, MOF, ARDS, sepsis, intra-abdominal complications, thromboembolic complications, and compartment syndromes. For those subjects meeting the highest risk subset inclusion criteria detailed in Section 6.3.1, direct data collection by the 24/7 RAs in addition to trauma registry data will be collected. Direct data collection will include prehospital information obtained from the run sheets and/or prehospital clinical staff, such as prehospital transport time, lifesaving interventions, blood product usage, fluids, hemorrhage control devices and vital signs. In-hospital data will include time to hemostasis, lifesaving interventions, blood product usage, fluids, vital signs, routine clinical laboratory results (including indices of shock and coagulation such as TEG, INR, base and lactate), diagnostic tests and interventional procedures. Blood product information (both pre and in-hospital) will include the amount, type, and expiration date of blood products and concentrates. All procoagulant medications and hemorrhage control devices used for improved hemostasis will also be collected. Examples of these interventions include, but are not limited to, TXA, PCCs, fibrinogen concentrate, junctional hemorrhage control devices, all types of tourniquets, XStat, REBOA, etc. These adjunct procedures and products may be utilized both prehospital (prior to transport or during transport) or in the hospital Amount of prehospital blood products and concentrates wasted because of deployment on helicopters will also be collected. Specific guidelines for data collection will be outlined in the MOO.

Discharge/death information collected on all enrolled subjects will include date and time of death or discharge, cause of death, hospital length-of-stay, number of ICU-free and ventilator-free days, final/discharge diagnosis, and discharge destination (i.e. home, long term care facility, rehabilitation facility, skilled nursing facility). All patient deaths will be assigned to one or more of the following groups: Exsanguination/Hemorrhagic Shock, Traumatic Brain Injury, Respiratory/Pulmonary Contusion, Tension Pneumothorax, Sepsis, Multiple Organ Failure, Cardiovascular Event, Pulmonary Embolism, Transfusion Related Fatality, or Other/Unknown. Subjects may have more than one cause of death. In an event of a patient death within 30 days following ED admission, the local site PI will determine the cause of death and provide a brief death summary. The cause of death assessment will be forwarded to the HDCC for review and adjunction by the Houston clinical site PI.

All data will be collected utilizing a standardized case report form. Each subject will be assigned a study-specific number and no identifying data will be entered into the secure web-based database. After data collection, all information will be entered into a web-based, secure data system designed for this study. We will leverage the system utilized in the PROPPR study. The web-based program will provide the flexibility of entering data from multiple locations and centralization of the data management process. To ensure security is maintained at all times, each user will be assigned a username and password. The username and password and time of each login will be recorded in a login history file to ensure a record is maintained of each access to the system. This information will also be recorded in the change history audit logs. The data entered for the PROHS study will be maintained in a secure database at the HDCC.

In addition to the unique information collected during the subject's hospitalization, the participating site's trauma registry department will provide their existing TQIP data. Sites will collect data that is in addition to, but not a duplication of, their existing TQIP data entry. TQIP collects 160 standard data elements on all trauma

patients, allowing robust risk adjustment between participating trauma centers. As much as possible the TQIP registry data at each site will be leveraged, minimizing the double collection of standard trauma data. We have confirmed that TQIP (personal communication with Dr. Avery Nathens) will provide state-of-the-art risk adjustment among participating centers.

8. Study Outcome Measures:

8.1. Primary Outcome:

The primary outcome will be in-hospital mortality. In an unpublished single site retrospective study of prehospital blood transfusions, 30-day in-hospital mortality was 34% among patients who received prehospital blood products.

8.2. Additional outcomes of interest:

Additional outcomes of interest include time to hemostasis, hospital length-of-stay, number of ventilator-free and ICU-free days, incidence of major surgical procedures, complications (TRALI, AKI, MOF, ARDS, sepsis, intra-abdominal complications, thromboembolic complications, compartment syndromes), lifesaving interventions, the amount and type of blood products and concentrates transfused (including prehospital), wastage of prehospital blood products and concentrates, use of external and internal hemostatic devices, and functional status at discharge/discharge destination.

9. Projected Enrollment:

9.1. Availability of Study Population:

We have received preliminary estimates of the source population from potential sites. Using an average of 473 patients/year transported by air ambulance at each potential site, we expect over 7000 at risk patients at ten participating sites during an 18-month enrollment period. We will collect registry data on all these patients. Additionally, we expect 15% percent of this population to potentially require blood products prehospital,[25, 32] resulting in approximately 1000 patients meeting highest risk inclusion criteria (the population of focus in this study). Based on our experience with three consecutive multicenter transfusion studies over the last eight years (totaling 70,000 screened and > 2500 transfused and enrolled patients) the mortality among the sickest patients (those who receive prehospital blood products), mortality will reach 34%.

9.2. Timeline:

We estimate PROHS to run over a 3 year time period which includes a 6 month start-up period followed by an 18 month enrollment period followed by a 1 year data analysis period.

Activities	**Period 1 6/14 – 12/14**	**Period 2 1/15-12/15**	**Period 3 1/16-12/16**	**Period 4 1/17-6/17**
Planning	✔			
Site Training	✔			
IRB approval	✔			
Enrollment		✔	✔	
On-going Data Analysis		✔	✔	✔
Study Close-out				✔

9.3. Sample Size:

The primary hypothesis of this clinical study is that patients with severe traumatic injuries who are evacuated to a Level I trauma center on air ambulances and who receive plasma and/or red blood cells (RBCs) (Group 1) will

have lower in-hospital mortality compared to patients evacuated on an air ambulance and who don't receive any prehospital blood products (Group 2).

Preliminary data indicates that we can expect Group 1 to experience an in-hospital mortality rate of 34%.[32] The mortality of the untreated group is unknown because of the difficulty in validly estimating mortality among patients who are at highest risk of death due to hemorrhage in the prehospital setting. The mortality rate provided is from a study performed at Memorial Hermann Hospital (MHH) in Houston, where blood products have been available on helicopters for two years. In this study, helicopter-transported patients who did not receive blood products were not as severely injured as helicopter-transported patients who did and therefore the estimate of mortality for this group is not accurate for patients at highest risk of bleeding to death. There has been no study to date that prospectively identifies patients at high risk of death due to hemorrhage during prehospital transport. One of the goals of this observational study is to accurately estimate mortality in the untreated group for use in designing a future clinical trial of prehospital blood transfusion. Finally, because this is an observational study of all available patients within 12-18 months, we will perform posterior power calculations to assess whether our preliminary sample size and mortality estimates were reasonable.

Based upon calculations found in Section 9.1, Availability of the Study Population, we expect a total sample size of 1000 patients. This number includes patients who receive blood as well as highest-risk patients who do not receive blood. Assuming that the patients who receive blood and those who do not receive blood will be distributed equally (500 in each group), we will have 90.1% power to detect a clinically meaningful difference of 10%, given a two-sided test of difference in proportions with an α-level of 0.05. This assumes no loss to follow up.[34]

10.Analysis Plan:

We will analyze in-hospital mortality as a fixed point in time using a Mantel-Haenszel statistic stratified by site. We will also test homogeneity of the risk ratios across sites using the Breslow-Day test. We will compute 95% confidence intervals on mortality by group. To provide further insight we will compute Kaplan-Meier survival curves.[36] To compare survival between groups, we will use Cox proportional hazards regression,[37, 38] adjusting for confounders. We will further explore heterogeneity by site and consider adjusting for site as a covariate or a random effect in any regression model as appropriate. Additional site-level covariates will also be considered if they are found to contribute to a difference in effect by site. Before interpreting the Cox analyses, we will test for proportional hazards. Further details can be found in the statistical analysis plan.

Covariate Adjustment

We will compare hazard rates for mortality between groups adjusting for confounders. If heterogeneity by site is evident, we will adjust for site as a random effect or adjust for other site-level variables in multi-level models if necessary. All patient characteristics and interventions present and ascertained during prehospital transport are eligible to be included as a confounder. We will screen the following variables as potential confounders: age, gender, race/ethnicity, trauma center, severity and type of injury, prehospital vital signs and laboratory results, platelets and other pre-hospital blood product components, procoagulants and prehospital interventions (e.g., external and internal hemostatic devices, etc.). In a previous observational multicenter trauma transfusion study,[26] identified confounders included: age, total blood product units transfused, injury severity score, site of bleeding, and trauma center.

In addition to the primary analysis proposed we will explore the use of propensity score matching[39,40] to adjust for confounding variables that might affect the mortality of those patients receiving prehospital blood products vs those who did not.

10.1. Exploratory cost assessment analysis:

We will perform a "piggy-back" economic study on the study. This will include the collection of ICD-9 code data that will allow estimation of severity-specific cost of an admission. We will use decision analysis modeling to estimate lifetime economic cost and consequences expected for the outcomes subgroups within the study.

10.2. Trauma Quality Improvement Program (TQIP):

We will facilitate data exchange with TQIP, who will provide state-of-the-art risk adjustment among participating centers as an exploratory analysis.

10.3. Exploratory analysis of overall at risk population:

Exploratory data analyses making use of the larger data set for the entire at-risk study population will examine overall between-group differences in mortality adjusted for injury and bleeding severity covariates (e.g., by direct standardization and multivariable Poisson regression). In this analysis, group A is defined as sites with pre-hospital blood products available and group B is defined as sites without pre-hospital blood products available.

11.Data Management:

All subjects will be identified by a study number only. All hard copies of source documentation will be kept in a secured, locked cabinet in a secure area. All electronic copies of source documentation will be maintained on a secure password computer. The study specific electronic data will be entered and maintained on a password protected web-based program designed for this study. All study documents will be maintained at the sites for at least two years after study completion unless superseded by participating site's requirements.

The data entered for the PROHS study will be maintained at the HDCC in a relational database cluster. The cluster is composed of multiple servers, which provide redundant access to the data in the event of a hardware failure to one of the servers. This cluster is maintained behind a firewall, which is not accessible from the internet without a secure network connection. The data will be backed up nightly and copies of the data will be routinely stored off site in a secure vault. In addition to the data servers, the production web server will also be backed up routinely. The separate development web server will serve as a backup to the production server.

11.1. Error Checking:

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Checks will be developed by clinical investigators. Depending on the question, any item found that does not meet the respective edit criteria will have an appropriate error message displayed when the user tries to save the data. Errors will be classified as either "hard" errors meaning that a valid response is required before the data can be saved or as "soft" errors in which the entry operator can either correct the errors or override them to indicate that the data are correct although it does not meet the edit criteria. Examples of hard errors would be items such as identifiers and event dates. An example of a soft error would be values that are outside a pre-defined range. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are currently four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors. For the first status, the entry user will have the option to save a record as "incomplete" for situations where they have partially entered a form and must stop because of an interruption. This will allow the user or the study coordinator to pull up the form at a later time and finish completing it. If the form was entered without any errors, then the record will be saved as complete. If the user overrides any soft errors found, the record will be saved as "saved with errors." Staff in the HDCC will have web-access to listings of subject specific errors needing correction by site. These errors can be corrected at the site or in the offices of the HDCC (given documentation of the change). All site investigators will be trained to

follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once an error has been corrected or certified as accurate by the site, the status will be change to "complete with errors." Once a record has been saved by the site or HDCC as complete, they will no longer be allowed to make changes to the records. Any changes that result from obtaining new information would be made by the staff at the HDCC. At the end of the study after all possible corrections are made, the database will be locked and further changes will not be made.

11.2. Correction Follow-ups:

Since there are times when data does not meet the required edit criteria such as out of range values, the sites still need to be able to save their data. However, such errors need to be followed up to ensure that the error was not by mistake. In this case, any soft error indicated will be logged to an error log data table through which the clinics can later generate a report of these errors that must be followed up on. This report will include the option for the user to enter the correct value(s) if the record was saved by mistake or to indicate that the value saved was correct in which case they must provide an explanation as to why the error was overridden. These reports must be transmitted back to the HDCC where staff will process the corrections through an error log management system. This process is particularly important for clarifying missing data. Once these reports are received back by the HDCC staff and processed, the respective data record will be updated to the forth status of "complete with errors." Since clinical staff must sign these reports, these reports will serve as audit records should the funding agency need to investigate the process.

11.3. Investigator Resources and Reporting:

A secure website will be provided through which authorized study management personnel, study investigators and coordinators, and representatives of the funding agencies can log in to review study recruitment status and other administrative reports about the study conduct and data quality.

11.4. Archiving the Final Dataset for Public Use:

Once the database is locked for analyses and primary study publications are completed, the HDCC will follow NHLBI guidelines related to archiving de-identified data and making it publically available when requested by the NHLBI.

12. Quality Assurance:

12.1. Protocol Approvals

The Resuscitation Outcomes Consortium (ROC) has developed a detailed process for generation, evaluation, implementation, and monitoring of protocols. The PROHS protocol is a ROC protocol, and once the protocol is approved by ROC (PRC and DSMB), site IRBs/REBs will review it. Additionally, ongoing protocol review of study progress by the ROC Management, Trauma and Executive Committees will occur. Detailed functions of all the above can be found on the ROC website https://roc.uwctc.org/tiki/tiki-index.php. The local IRBs/REBs provide additional regulatory oversight.

12.2. Training:

Training of the research team (i.e. investigators, nurses, coordinators, assistants) who will be responsible for screening and following the enrolled subjects will be provided through webinars, conference calls, and in-person as applicable. A standard manual of operations will be provided with standard definitions of all study variables and guidance for the data collection and entry processes. Copies of the manual will be provided to all participating sites. In addition to the training provided by the PROHS coordinating team, each site will be responsible for the complete education and training of their study personnel for the PROHS study.

12.3. Study Monitoring

Sites will be trained and monitored throughout the course of the study by members of the PROHS coordinating team. Each site not previously involved with ROC will be visited to certify that the site is ready to begin. A standard manual of operations developed by the Houston clinical site and HDCC will provide standard definitions of all study variables (i.e., data elements) and describe all data collection and data entry procedures in detail. In addition to any initial training meetings, each site will be responsible for the complete education of their personnel in the conduct of the PROHS study. Site visits will occur as needed.

13. Administrative Structure:

The PROHS study is one of several studies currently being conducted by ROC. The ROC Data Coordinating Center (DCC) is responsible for clinical and data coordination for all ROC studies. The UTHealth Houston clinical site and the UTHealth Data Coordinating Center (HDCC) are satellites of the ROC DCC under a separate sub-contract for purposes of the PROHS study with the majority of the work being carried out by these satellites. The Houston clinical site will oversee all clinical sites. The HDCC will perform data collection activities. To foster collaboration key personnel from the ROC DCC and Houston clinical site and HDCC will meet on a regular basis. PROHS progress will be reported routinely at Trauma, Management and Executive Committee calls. The Houston clinical site and HDCC conduct the sub-contracts in accord with ROC governing procedures and NHLBI policies and guidelines.

14. Human Subjects Research:

14.1. Risks to Subjects:

This study poses no more than minimal risk to the subjects. The only potential risk is the possibility of breach of confidentiality. All measures will be taken to ensure that patient confidentiality is maintained. Hard copy source documents will be kept in a locked cabinet in a locked office or area. Electronic source documentation will be maintained on a password protected computer. All study specific data will be entered into a web-based, password protected computer program. Only study staff specifically dedicated to the study will be provided with a username and password for the data entry process as discussed in the Study Data Collection Process section.

14.2. Risk Management and Emergency Response:

Subject participation in this study poses no more than minimal risk. PROHS is an observational study, therefore participation in this study will not change the care provided to the subject. All care will be directed per the standard of care policies implemented at each participating site.

14.3. Potential Benefits:

There are no direct benefits to the subjects enrolled in this study, however there is potential benefit to future trauma patients. The information obtained from this study will provide the clinical team data to support the development of future prospective and randomized trials of prehospital resuscitation.

14.4. Source of Data Collection:

Data will be collected prospectively during the study. This will include a daily review of the medical records and results of diagnostic studies. A description of the data collection process is detailed in the Study Data Collection Process section.

14.5. Waiver of Informed Consent:

This study will be comparing two established methods of resuscitation that represent local standards of care. We are requesting a waiver of informed consent for the subjects enrolled in this study for the following reasons as identified in OHRP 45 CFR 46.116(d):

1. The research involves no more than minimal risk to subjects.
   Rationale: This is a pragmatic, prospective, observational study. There will be no patient contact through the duration of the study. Also, there will be no study intervention or procedures involved. All subjects will be cared for according to the participating site's standard of care policies and procedures. All data collected for the purposes of this study will be done through direct observation, medical record review or trauma registry.

   The only potential risk is possible breach of confidentiality. All study data will be entered into a password protected web-based program. A username and password will be issued to each individual identified as working with the study at all sites. A log will be maintained the user activity throughout the study. All source documentation will be kept in a secure area or on a password secure computer.

   All subjects will receive a specific study number for study data entry. A master linking log will be kept at each site in a secure area. The study coordinating team will not access this log.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
   Rationale: Waiver of consent will not adversely affect the rights and welfare of the subjects. The information collected during this study will not change or impact the care the subject receives.

   The purpose of this study is to observe and document current prehospital resuscitative regimens and hospital outcomes at the participating centers. The information gained from this study will assist clinicians in implementing changes to treatment regimens after study results are finalized to potentially improve clinical practice and improve outcomes for severely injured trauma patients.

3. The research could not practicably be carried out without the waiver or alteration.
   Rationale: This study cannot be practicably carried out without waiver due to the nature of the injuries or the altered mental state the subject is in upon arrival to the ED. Patients considered eligible for this study have sustained multiple, serious injuries and are often unconscious, intubated and/or sedated heavily and unable to comprehend or provide an informed decision to participate.

   Legally Authorized Representatives (LARs) are often not available at the time of subject's arrival to the ED and frequently not available for several hours after the injury.

4. Whenever appropriate, the subjects will be provided with additional pertinent information.
   Rationale: Results of the study will be shared with the participating site's principal investigators and study team at the end of the study. This information will allow the site investigators to amend their current resuscitation regimens as they deem necessary.

14.6. Vulnerable Populations:

While the NIH considers anyone under the age of 21 to be a part of the pediatric research group, there is wide variability in state laws defining the adult population. Taking this wide variability into consideration, all consent related procedures, forms, and notification documents will be approved by the participating site's local IRBs prior to the onset of the study.

This study may include subjects age 15 to 20. Patients fifteen years of age and older are considered adult in a large percent of the trauma centers. Sixteen and seventeen year olds are able to drive in most states and are at

high risk for motor vehicle accidents resulting in blunt or penetrating injuries. It is difficult to differentiate a 16 or 17 year old from one who is 21 or older at the time care is initiated both in the prehospital setting and in the ED until positive identification can be obtained. Children below the age of 15 or 50 kg body weight will be excluded from this study. Children's intravascular volume is different than an adult's, requiring adjustments to the standard adult treatment protocols. In addition, this study will be conducted at adult Level I trauma centers which may or may not have affiliated pediatric programs.

Prisoners admitted to the ED from a correctional facility will be excluded from enrollment. It is possible that subjects who are under police observation as suspects may be enrolled into the PROHS study. These subjects will remain in the study until discharge or incarceration.

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