Table of Contents

ABBREVIATIONS

AE – Adverse Event
AHTRs - Acute Hemolytic Transfusion Reactions
AIS – Abbreviated Injury Scale
ARDS – Acute Respiratory Distress Syndrome
Cc – cubic centimeter
CPR – cardiopulmonary resuscitation
CRF – case report form
DSMB – data safety monitoring board
ED – emergency department
ELISA - Enzyme-linked immunosorbent assay
FFP – Fresh Frozen Plasma
GSW – Gun shot wound
HR – heart rage
ICF – informed consent form
ICU – intensive care unit
IND – investigational new drug
INR – international normalized ratio
IRB – institutional review board
IV - intravenous
LAR – Legally Authorized Representative
LTLR-WB - Low Titer, Leucocyte Reduced, Whole Blood
mmHg – millimeter of mercury
MOF – Multiple Organ Failure
NI – Nonsocomial Infections
non-WB – non- Whole Blood
PI – Principal Investigator
PLT -Platelets
PRBCs – Packed Red Blood Cells
PT – Prothrombin Time
PTT – Partial Thromboplastin Time
SAE – Serious Adverse Event
SBP – Systolic Blood Pressure
SOP – Standard Operating Procedure
TACO – Transfusion Associated Circulatory Overload
TEG - Thromboelastograph
TRALI – Transfusion Related Acute Lung Injury

PROTOCOL SYNOPSIS

Protocol Title:	Pragmatic, Prehospital Group O, Whole Blood Early Resuscitation trial (PPOWER)
Protocol Number:	PRO17100053
NCT Number:	NCT03477006
Version # and Date:	Version 7 Dated 2020-02-04
Clinical Phase:	Phase 3
Investigational Drugs:	Low titer, platelet replete-leukocyte reduced, group O whole blood
Trial Site:	University of Pittsburgh
IND Sponsor:	Jason L. Sperry, MD, MPH
Investigator:	Jason L. Sperry, MD, MPH
Co-Principal Investigator	Darrell J. Triulzi, MD
Sub-Investigators:	Frank Guyette MD, MPH; Matthew Neal, MD; Mazen Zenati, MD, PhD; Mark Yazer, MD
Research Facilities:	UPMC Presbyterian/ Montefiore
Clinical Laboratories:	UPMC Presbyterian Shadyside CP PUH- UPMC Clinical Laboratory Building
Study Rationale:	Initiation of whole blood resuscitation in the prehospital setting and continued through the in-hospital phase of treatment to patients in hemorrhagic shock represents the most efficacious and ideal intervention post-injury.
Study Objectives:	The objective of this study is to determine whether LTLR-WB resuscitation in the prehospital setting with continuation through the in-hospital acute resuscitation phase of care will significantly reduce the morbidity and mortality attributable to hemorrhagic shock post-injury as compared to standard prehospital and in-hospital resuscitation practice.
Study Hypothesis:	Early whole blood transfusion initiated in the prehospital setting and continued through the in-hospital acute resuscitation phase of treatment will reduce the morbidity and mortality attributable to hemorrhagic shock post-injury as compared to standard prehospital and in-hospital resuscitation practice
Study Aims:	Specific Aim I: Determine the feasibility and most appropriate study population that will lead to a large multicenter clinical trial designed to evaluate the effectiveness of prehospital through in-hospital LTLR-WB as compared to standard care practice in patients at risk of hemorrhagic shock. Specific Aim II: Determine if prehospital through in-hospital LTLR-WB reduces 28-day mortality, multiple organ dysfunction, presenting coagulopathy, 24-hour resuscitation requirements and early mortality time points as compared to

	standard of care prehospital and in-hospital resuscitation in patients at risk of hemorrhagic shock. Specific Aim III: Determine the primary drivers by which prehospital through in-hospital LTLR-WB improves clinical, resuscitative and hemostatic outcomes as compared to standard of care prehospital and in-hospital resuscitation in patients at risk of hemorrhagic shock.
Study Design:	The pilot study will be a 3-year, pragmatic, prospective, randomized, open label, pilot clinical trial utilizing a busy level 1 trauma center with one of the busiest air medical services in the country where affiliations with local blood bank colleagues exist to provide cold storage LTLR-WB for the prehospital (up to 2 units) and in-hospital setting (up to 6 additional units), up to 8 units total. There are 14 helicopter bases which fly patients to Presbyterian Hospital at the University of Pittsburgh.
Planned Sample Size:	56 patients in each arm, 112 total patients
Duration of Treatment:	3 Years
Major Inclusion Criteria:	1. Injured patients at the risk of Hemorrhage being transported from scene or referral hospital to a participating PPOWER trial site AND 2A. Systolic blood pressure ≤ 90 mmHg AND tachycardia > 108 bpm at scene, or at outside hospital or during transport. OR 2B. Systolic blood pressure ≤70 mmHg without tachycardia requirement, at scene or outside hospital or during transport.
Major Exclusion Criteria:	1. Documented age: Age ≥90 or <18 years of age 2. Inability to obtain intravenous or interosseous access 3. Isolated fall from standing injury mechanism 4. Known prisoner or known pregnancy 5. Traumatic arrest with > 5 minutes of CPR without return of vital signs 6. Brain matter exposed or penetrating brain injury (GSW) 7. Isolated drowning or hanging victims 8. Isolated burns without evidence of traumatic injury 9. Referral Hospital In-patient admission 10. Objection to study voiced by subject or family member at scene 11. Wearing PPOWER opt-out bracelet
Study Endpoints:	The primary endpoints of this study are 1.) 28-day all-cause mortality as the safety and efficacy endpoint; 2.) enrollment and accrual rate as the feasibility endpoint.

1. OBJECTIVE, SPECIFIC AIMS, BACKGROUND, AND SIGNIFICANCE

1.1 OBJECTIVE

The objective of this study is to determine whether LTLR-WB resuscitation in the prehospital setting with continuation through the in-hospital acute resuscitation phase of care will significantly reduce the morbidity and mortality attributable to hemorrhagic shock post-injury as compared to standard prehospital and in-hospital resuscitation practice.

1.2 SPECIFIC AIMS

Hypothesis: The initiation of LTLR-WB resuscitation in the prehospital setting with continuation through the in-hospital acute resuscitation phase of care will significantly reduce the morbidity and mortality attributable to hemorrhagic shock post-injury as compared to standard prehospital and in-hospital resuscitation practice.

Specific Aims:

Specific Aim I: Determine the feasibility and most appropriate study population that will lead to a large multicenter clinical trial designed to evaluate the effectiveness of prehospital through in-hospital LTLR-WB as compared to standard care practice in patients at risk of hemorrhagic shock.

Specific Aim II: Determine if prehospital through in-hospital LTLR-WB reduces 28-day mortality, in-hospital mortality, multiple organ dysfunction, presenting coagulopathy, 24-hour resuscitation requirements and early mortality as compared to standard of care prehospital and in-hospital resuscitation in patients at risk of hemorrhagic shock.

Specific Aim III: Determine the primary drivers by which prehospital through in-hospital LTLR-WB improves clinical, resuscitative and hemostatic outcomes as compared to standard of care prehospital and in-hospital resuscitation in patients at risk of hemorrhagic shock.

1.3 BACKGROUND and RATIONALE

Traumatic injury represents an incredible health care burden in the United States and worldwide.[1] Hemorrhage is estimated to be responsible for over 40% of all trauma-related deaths.[2,3] Ongoing traumatic blood loss is complicated by the well-known 'lethal triad' of coagulopathy, hypothermia and acidosis which results in further unbridled hemorrhage.[4-11] Uncontrolled bleeding, resultant shock and organ dysfunction remain the leading causes of early in-hospital mortality.[12,13] Despite advances in trauma resuscitation, a paucity of therapeutic interventions are available early enough to reduce the downstream morbidity and mortality attributable to hemorrhage, shock and coagulopathy.[14,15]

In-hospital resuscitation of traumatic hemorrhage has changed over the past decade.[16-21] The underlying principle of current resuscitation practice focuses on preventing or reversing the effects of coagulopathy with the early use of a balanced component transfusion strategy (1:1:1 - plasma: packed red blood cells: platelets).[22] This reconstituted strategy has also been coined 'whole blood-like' resuscitation despite being inferior compositionally to whole blood.[23,24] The use of whole blood was historically the gold standard for treating hemorrhagic shock during World War I and II, prior to sweeping changes in blood banking practice.[25] Whole blood use continues today and is thought to provide the bleeding patient the identical components they are losing with maximal resuscitative and hemostatic effects.[26-30]

Recent military experiences continue to show the benefits of fresh whole blood resuscitation demonstrating significant survival and hemostatic advantages.[31-34] Whole blood has also been

postulated to improve microcirculatory hemodynamics, reduce the 'storage lesion' effect and minimize donor exposure risks.[35] A recent civilian study has also demonstrated benefit using modified whole blood after arrival to the hospital where appropriate blood typing and cross matching was performed prior to transfusion.[36] Due to the time sensitive nature of the treatment of hemorrhage, the ideal resuscitation intervention would entail use of a blood product containing all essential hemostatic components, closest to time of injury, where prevention or reversal of the devastating downstream consequences of shock and coagulopathy can occur.

Initiation of whole blood resuscitation in the prehospital setting and continued through the in-hospital phase of treatment to patients in hemorrhagic shock represents this ideal intervention post-injury. Essential to the prehospital initiation of whole blood resuscitation in the civilian population is need for it to be transfused without the need for blood typing or cross matching. Of similar importance is the need for cold storage and recycling of any unused whole blood product, allowing maximal utility of this precious resource.

We hypothesize that the initiation of LTLR-WB resuscitation in the prehospital setting with continuation through the in-hospital acute resuscitation phase of care will significantly reduce the morbidity and mortality attributable to hemorrhagic shock post-injury as compared to standard prehospital and in-hospital resuscitation practice. Thus, a large pragmatic clinical trial is needed to definitively establish the efficacy and safety of whole blood resuscitation initiated in the prehospital setting. Only a high-quality clinical trial will provide the essential evidence to justify and provide the impetus for the use of this precious blood banking resource early post-injury. Because of the challenges associated with execution of these types of large trials particularly in the prehospital setting,[38] it is essential to establish feasibility of this approach in a pilot study and provide experience to inform a definitive large, multicenter whole blood trial.

1.4 INNOVATION

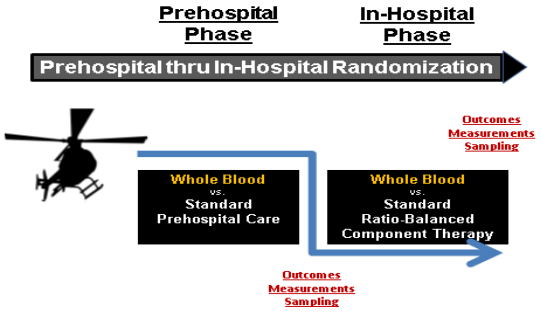


Fig 1. Study Organization

Interventions that are initiated in the prehospital setting represent the forefront of traumatic injury research. The majority of such prehospital trauma trials are performed under the requirements of *exception from informed consent for emergency research* with regulatory oversight by the Food and Drug Administration (FDA) and Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24). Although the additional regulatory requirements of this type of research remain extremely arduous, the beneficial consequences of providing novel interventions during the earliest phase of treatment, within minutes from the time of injury, cannot be overstated. Treatment of hemorrhage is time sensitive[79,80]. The ability to initiate early whole blood resuscitation, containing all essential hemostatic components, at a time point where prevention or reversal of the downstream manifestations of shock and coagulopathy can occur is of paramount significance. It is this early prehospital therapeutic window where a reduction in the morbidity and mortality which complicates traumatic injury can be potentially realized.

Another innovative aspect of the proposed trial is the essential collaborative and multidisciplinary approach required to execute a prehospital initiated whole blood resuscitation interventional trial. Group O whole blood represents a precious resource to blood banks across the country. Essential to the clinical investigation of early whole blood resuscitation post-injury and the ultimate integration of whole blood into standard trauma practice is the collaborative relationship between trauma surgeons, blood banking specialists and prehospital administration and providers. It is this cohesive and cooperative rapport that maximizes patient benefit

concurrently with appropriate blood product resource utilization.[37] It will be the successful execution of this pilot trial that will provide the backdrop and impetus for these collaborative relationships to develop at other institutions.

Whole blood transfusion following traumatic injury represents the 'essential next step' for the management of hemorrhagic shock post-injury. The potential significance of whole blood being provided in the prehospital setting brings this potential lifesaving hospital intervention to those patients who need it most, at the most beneficial time before hemorrhagic shock and coagulopathy begin to have their detrimental consequences.

1.5 SIGNIFICANCE

Early whole blood resuscitation has significant potential to prevent downstream manifestations of shock and coagulopathy, attenuate glycocalyx injury, improve microcirculatory hemodynamics and provide the most hemostatic and definitive resuscitation available.[24,35,42,43] It is the ability to initiate needed whole blood in the prehospital setting to those patients who would benefit most, at the earliest time post-injury, before hemorrhagic shock and coagulopathy can result in their detrimental consequences, which underscores the significance of the impact of the study.

The University of Pittsburgh, Presbyterian Hospital has over the last 2 years initiated an urgent release whole blood transfusion program for trauma patients in hemorrhagic shock in our emergency department utilizing LTLR-WB identical to the proposed intervention for the pilot and large multicenter trial. We published data on the first 47 patients demonstrating the feasibility and initial safety of such a program.[28] We have continued this program and have currently utilized LTLR-WB in over 187 patients with no safety concerns. We have simultaneously been monitoring LTLR-WB patients for hemolytic side effects from ABO mismatched whole blood.[29] In 27 non-group O patients, there were no significant differences in laboratory hemolysis markers. These preliminary and published data verify the feasibility and safety of this type of intervention in patients with hemorrhagic shock, providing the backdrop for the successful execution of the proposed pilot trial and future large multicenter trial.

The most obvious driver of potential outcome benefits for early LTLR-WB transfusion is that the hemorrhaging patient is receiving a robust resuscitative and hemostatic product identical in composition to what they are losing with the potential for a lower risk of coagulopathy. Early whole blood resuscitation has potential additional benefits which may drive outcome differences in those with hemorrhagic shock. Whole blood has been hypothesized to improved microcirculatory hemodynamics, reducing the sequelae of shock and anaerobic metabolism.[35,68-71] Increasing evidence suggests that platelet function may be maintained or even improved with cold storage providing further hemostatic benefit.[61,65] Plasma resuscitation alone or in conjunction with whole blood has increasingly been shown to benefit endothelial glycocalyx integrity and homeostasis.[42,72] Importantly, plasma resuscitation has been shown to reduce Syndecan-1 shedding, an endothelial glycocalyx constituent whose levels are known to be associated with inflammation and coagulopathy.[43,72,73] Additional benefits may include minimization of donor exposure, as the requirements for whole blood storage and resuscitation would lower overall age of the transfused products as compared to balanced component resuscitation. [24,35,45,46]

2. RESEARCH DESIGN AND METHODS

2.1 CLASSIFICATION AND METHODOLOGICAL DESIGNS

The pilot study will be a 3 year, pragmatic, prospective, randomized, open label, clinical trial utilizing a busy level 1 trauma center with one of the busiest air medical services in the country where affiliations with local blood bank colleagues exist to provide cold storage LTLR-WB for the

prehospital (up to 2 units) and in-hospital setting (up to 6 additional units), up to 8 units total. There are 14 helicopter bases which fly patients to Presbyterian Hospital at the University of Pittsburgh. Some of the busiest air medical bases in the system will be utilized for the pilot trial. The pilot trial may need fewer or more bases added as enrollment proceeds. The study is required to be open label due to the inability to blind blood or blood component transfusion.

2.2 DETAILED DESCRIPTION OF STUDY DESIGN

Study Population: The study population will consist of injured patients at risk of hemorrhage being transported via air medical services from the scene of injury or from referring hospital to a definitive care trauma center participating in the PPOWER pilot trial. Patients will be enrolled in the prehospital setting prior to trauma center arrival with continuation of LTLR-WB resuscitation or standard of care resuscitation during the in-hospital acute resuscitation phase of the study.

Study Population Rationale: The most appropriate patient population who would benefit most from early, prehospital initiation of LTLR-WB are those with potentially survivable injuries, at risk of the detrimental complications attributable to hemorrhagic shock, using criteria which can be widely generalizable in the real-world prehospital setting. In the prehospital phase of treatment, complete characterization of injuries and injury severity is not possible. We have chosen inclusion and exclusion criteria based upon preliminary data obtained from the PAMPer study, a recently closed pragmatic prehospital trial at the University of Pittsburgh.[40] The incidence of arrival shock (87%) and coagulopathy (41%), the need for large volume transfusion (36%) and the development of multiple organ failure (25%) and overall mortality (30%) utilizing the proposed inclusion and exclusion criteria, with appropriate modifications, will provide the most appropriate patient population to demonstrate the benefits of LTLR-WB resuscitation.

Group O whole blood represents a precious blood banking resource. There exists an even further limited supply of Rh negative, group O whole blood (6.6% of blood supply overall). Due to this supply limitation, the only feasible and sustainable approach for whole blood resuscitation is to utilize Rh positive group O whole blood, which is significantly more common (37.4% of blood supply overall).

2.3 STUDY INTERVENTION

The study intervention will be the initiation of prehospital through in-hospital transfusion of LTLR-WB in patients meeting all inclusion and no exclusion criteria. Whole blood units will be obtained from a local FDA licensed blood center (LifeSource dba Central Blood Bank; Registration number: 2571073; License number: 1025).

Up to two units of LTLR-WB (O+) will be initiated in the prehospital phase of the study with an additional 6 units of LTLR-WB (O+) available during the in-hospital phase of the trial if indicated.

Study Intervention Rationale: To provide the earliest and most robust intervention with appropriate concern for blood banking resource utilization, a prehospital and in-hospital phase intervention will be utilized. As whole blood resuscitation is most pertinent to patients with acute hemorrhage, we have limited the in-hospital acute resuscitation phase time period and the additional 6 units of LTLR-WB to 4 hours post-admission. This acute phase resuscitation period definition is based upon unpublished data from the recently completed PAMPer study at our institution.[40] Over 79% of the blood products transfused in the first 24 hours occurred in the first 4 hours following admission.

Whole Blood Intervention: Blood from male only, group O+ donors will be collected using the FDA approved Terumo Imuflex® WB-SP blood bag system. With this collection system, whole

blood passes through a platelet sparing inline leukoreduction filter into a bag containing citrate phosphate dextrose solution. Male only whole blood donors will be used in order to mitigate the risk of transfusion related acute lung injury (TRALI; estimated incidence ≈1:12,000). Whole blood collected with this system can be kept as such for up to 21 days when stored between 1-6ºC. Per blood bank protocol, the anti-A and anti-B antibody titers in each unit will be tested on a sample from every donor using an immediate spin saline tube method without incubation; only units where the titer of both anti-A and anti-B are **<100** will be issued for the study and subsequent transfusion. All other required transmissible disease testing will also be performed on these LTLR-WB units before they are released, as per blood bank standard practice. The LTLR-WB units will have affixed on them the standardized Whole Blood product label thereby making them easily distinguishable from the other non-WB units in inventory.

2.4 INTERVENTIONAL ARM

Prehospital Phase Interventional Arm: Two units of LTLR-WB (O+) will be stored at each helicopter base in temperature regulated blood bank approved refrigerators for up to 14 days, which is the period within which cold stored platelets are thought to retain maximal function. Two units of LTLR-WB will be transported on all air medical flights with prehospital staff in blood banking approved and verified coolers. The temperature of the blood will be monitored throughout transit and storage in accordance with standard blood banking and Stat MedEvac procedures. Following 14 days without use, LTLR-WB will be replaced with new LTLR-WB units and the old products will be returned to the blood bank for recycling into PRBCs.. During transport, storage and during all flights standard STAT MEDEVAC protocols for storing and carrying blood products at the base and on the helicopters will be followed. While at the bases the blood units are stored in a dedicated blood refrigerator and moved to cooler for transport only when the aircraft is launched. The blood is packaged in the coolers with a thermometer for temperature maintenance to assure that they are maintained at 2-5 degrees Celsius at all times. The Clinical Protocol that is currently followed and will be followed for all blood products in the study can be found in **Appendix 1.** Our FDA approved blood bank will follow all regulations required by the FDA for safe blood and blood component transfusion. On day 15, after ensuring the WB unit had remained in temperature compliance and is otherwise eligible for recycling according to 21 CFR 640.2(c), the WB unit will be recycled into a PRBC unit following the standard operating procedures at the Centralized Transfusion Service in Pittsburgh.

Patients who meet all inclusion and no exclusion criteria at the scene, at a referral hospital or during transport and are randomized to the interventional arm will receive up to 2 units of LTLR-WB (O+) en-route to a PPOWER participating trauma center based upon hemodynamic status using identical criteria as the Prehospital Standard of Care arm. If the intervention is completed during transport, standard operating procedures for the prehospital setting will be employed by the prehospital providers during the remaining flight. **(Appendix 7)**

In-Hospital Phase Interventional Arm: Once enrolled in the interventional arm, prehospital providers will inform the trauma team of PPOWER enrollment and the randomization of the patient into the interventional arm (LTLR-WB administration arm). Upon arrival and on-going in-hospital LTLR-WB transfusion will be at the discretion of the trauma attending/team based upon the hemodynamic status of the patient, injury severity, need for therapeutic intervention, control of hemorrhage and on-going coagulopathy.

Patients enrolled in the interventional arm will only receive LTLR-WB if blood products are required during the acute resuscitation phase over the first 4 hours following admission (up to 6 units of LTLR-WB). The acute resuscitation phase generally includes the first 4 hours from the time of admission. Six units of LTLR-WB will be available for urgent release in the emergency department and will be taken to the operating room as needed. In those patients with ongoing

hemorrhage who require blood products beyond the 8 units of LTLR-WB total (2 prehospital, 6 in-hospital), a balanced component transfusion strategy will be employed identical to the standard of care arm of the study and usual care at the University of Pittsburgh.

2.5 STANDARD OF CARE ARM

Prehospital Standard Care Arm: Patients who meet all inclusion and no exclusion criteria at the scene, at a referral hospital or during transport and are randomized to the standard of care arm of the study will receive resuscitation fluids, including crystalloid and PRBC infusion, per the current standard practice.

In-Hospital Standard Care Arm: Once enrolled in the standard of care arm, prehospital providers will inform the trauma team of PPOWER enrollment and standard of care arm assignment upon arrival and on-going in-hospital blood component transfusion will be at the discretion of the trauma attending/team based upon the hemodynamic status of the patient, injury severity, need for therapeutic intervention, control of hemorrhage and on-going coagulopathy. Patients enrolled in the standard of care arm will receive products using a balanced component transfusion strategy (1:1:1 - fresh frozen plasma: packed red blood cells: platelets)[22] with TEG directed adjustment if blood products are required for on-going resuscitation.[82] Four units of uncrossmatched PRBCs will be available for urgent release in the emergency department. (**Figure 2**)

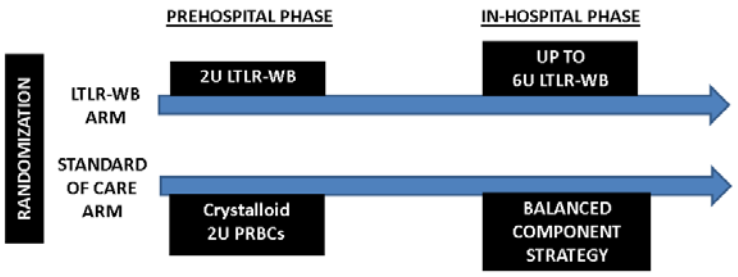


Fig 2. Schematic depicting randomization arm comparison

2.6 RANDOMIZATION

Procedures Assuring Adherence to Randomized Assignment: Enrollment will occur in the prehospital phase of the trial and LTLR-WB or prehospital standard of care will be provided based upon randomization assignment. Prehospital providers will designate the patient as enrolled and notify receiving staff of the treatment arm. Research staff will be present upon arrival and will communicate directly with blood banking staff/anesthesia and the trauma team regarding the randomization arm of the patient. Once in-hospital, LTLR-WB randomized patients may receive LTLR-WB transfusion as indicated during this acute resuscitation phase of in-hospital care up to 6 units in-hospital and 8 units of LTLR-WB total.

Randomization and Blinding: A single stage cluster randomization scheme will be utilized. Designated air medical bases at the University of Pittsburgh will be block randomized and assigned to the LTLR-WB arm or Standard of Care (control) arm for 1 month time intervals. The cluster design will be at the level of the helicopter base. The block scheme will vary randomly between 2 and 4 month block sizes over the period of enrollment for the trial. Randomization assignments will be determined prior to the start of the bases enrollment following the above single stage cluster design using standard computerized randomization software. Communication with the blood bank transportation services and each respective air base will occur and an annual schedule of randomization assignment will be distributed to each study air base. This specific randomization scheme is required due to the limited supply of O+ LTLR-WB and also due to the logistics and delivery of the intervention in the prehospital setting. The

proposed pilot trial will be an open label trial as blood product transfusion requires appropriate documentation and essential look back procedures.

2.7 STANDARD OPERATING PROCEDURES

Prehospital Standard Operating Procedures: The University of Pittsburgh Medical Center is being utilized for this pilot trial because it is a level I trauma center with busy air medical transport services that is recognized for providing high level care of the injured patients. To minimize over exuberant crystalloid resuscitation during the prehospital phase of treatment after enrollment and randomization, further crystalloid use will follow a 'goal directed' standard operating procedure based upon published evidence from our institution.[81]

In-Hospital Standard Operating Procedures: For the pilot trial once 4 hours has passed without ongoing blood transfusion requirements, standard transfusion practice evidence in the ICU will be followed including standard evidence based guidelines for each respective institution.[83]

Resuscitation Practice: Irrespective of randomized arm, resuscitation practice during the in-hospital phase of care will be based upon the patient's hemodynamic status, bleeding control status, laboratory analysis, physician decision making and/or coagulopathy. Although the current trial will characterize what is given (LTLR-WB vs. component resuscitation) during the acute resuscitation phase of management, indications, quantity, and the rapidity of blood product transfusion will be dictated by the clinical status of the patient as directed by the trauma and anesthesia teams as is done for all trauma resuscitations.

2.8 STUDY ENDPOINTS

Principle Outcomes: The principle objectives for the pilot trial are to evaluate 1.) safety and efficacy and 2.) feasibility for a prehospital through in-hospital LTLR-WB resuscitation protocol that will lead to a large, multicenter clinical trial that can be performed under the requirements of *exception from informed consent for emergency research* with regulatory oversight by the Food and Drug Administration (FDA) and Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24).

Primary Outcome For Assessing Safety and Efficacy: The primary safety and efficacy outcome for the pilot trial will be all cause 28-day mortality. We will utilize data derived from our recently completed PAMPer trial, which utilized identical inclusion and exclusion criteria, for in-hospital mortality estimates.

Primary Outcome For Assessing Feasibility and Trial Performance: The primary feasibility outcome for the pilot trial will be enrollment and accrual rate. Secondary performance and feasibility outcomes will include a) Eligibility rates; b) Adherence rates for the protocol; c) Injury and patient characteristics enrolled in the trial; d) Frequencies of proposed clinical outcomes; e) Air medical base population differences.

Secondary Clinical Outcomes Estimating Treatment Effectiveness and Safety: Over 28 days or up to discharge following randomization, we will compare: 1) Multiple Organ Failure (MOF): Organ dysfunction will be evaluated via the Denver Post-Injury Multiple Organ Failure Score and characterized as both a rate (%) and as MOF free days.[84,85] 2) Mean Denver Post-injury MOF Score: This continuous variable will be a much more sensitive measure of organ dysfunction for the pilot trial. 3) Arrival Shock Severity: We will compare presenting base deficit,

lactate and shock index (SI, heart rate/systolic blood pressure-bpm/mmHg) 4) Acute Respiratory Distress Syndrome (ARDS): We will compare pulmonary dysfunction using the Berlin definition for ARDS.[86] 5) Nosocomial Infection (NI): We will compare the incidence of pneumonia and blood stream infections. 6) Mortality: We will compare mortality rates at 3, 6 and 24 hours following arrival, all cause in-hospital and 28-day mortality. 7) Blood component transfusion and resuscitation requirements at 24 hours: We will compare overall blood component transfusion requirements and crystalloid/colloid resuscitation requirements across the two arms. 8) Acute Hemolytic Transfusion Reaction (AHTR): We will compare the incidence of AHTRs across study arms as defined by the CDC/National Healthcare Safety Network (NHSN) Hemovigilance Surveillance definition. (www.cdc.gov/nhsn) Length of hospital stay and intensive care unit stay. Length of stay and ICU resources will be descriptively compared. Patients will be followed for 28 days from admission for the 28-day mortality outcome utilizing chart review, patient contact or utilization of the social security death index for those who cannot be contacted.

Predefined Subgroup Analyses: Predefined subset analyses for the pilot trial will be performed looking at our primary outcomes (safety/efficacy and feasibility) in 1) Females > 50 years of age versus study cohort with females < 50 years excluded ; 2) Patients who ultimately did or did not require in-hospital blood transfusion; 3) Patients with and without significant traumatic brain injury (Head abbreviated injury score- AIS >2); 4) Patients enrolled from the scene of injury versus those enrolled from a referral hospital; 5) Patients that require operative intervention in the first 24 hours; 6) Those patients with a preinjury history of anticoagulation / antiplatelet therapy; 7) Patients who ultimately did or did not require massive transfusion (≥ 10 units blood in first 24hrs) 8)Patients who did or did not receive prehospital PRBCs.

Clinical Outcome Definitions:

Multiple Organ Failure (MOF)**:** Organ dysfunction will be evaluated via the Denver Post-injury Multiple Organ Failure Score, a well-validated scoring system in injured patients and characterized as an incidence rate (%) and as MOF free days.[84,87] Patients who are never admitted to the ICU or those with a length of ICU stay of less than 48 hrs will be considered to have a Denver score of 0. A summary of the Denver score may be calculated by summing the worst scores of each of the individual systems over the course of the ICU stay. A summary Denver score > 3 will be classified as MOF. Scores will be determined daily up until ICU discharge.[87] Mean Denver Post-injury MOF Score: As the primary endpoint for the pilot trial, the 3 highest (worst) daily Denver scores will be averaged and compared across the treatment arms. Patient not in the ICU will be given a score of 0. Acute Respiratory Distress Syndrome (ARDS): The Berlin definition for mild ARDS (PaO_2/FIO_2, ≤ 300 mm Hg + timing, imaging and origin criteria) will be utilized as a threshold value to determine the incidence of ARDS and will be further stratified into Moderate (PaO_2/FIO_2, ≤ 200) and Severe (PaO_2/FIO_2, ≤ 100).[86](Nosocomial Infection (NI): The CDC criteria for the diagnosis of hospital acquired pneumonia and blood stream infection will be utilized (www.cdc.gov/nhsn) Mortality: We will derive the time to a mortality event from the time of admission for 6 hour and 24 hour mortality rates over the initial 24 hours. All cause in-hospital and 28-day mortality will be similarly determined from the date of admission. 7) Blood component transfusion and resuscitation requirements at 24 hours: Blood component transfusion needs per unit (PRBC, FFP, PLT) will be recorded over the first 24 hours of admission with 6-hour incremental totals. For every unit of LTLR-WB that is transfused each will be designated as 1 unit of PRBC, 1u of FFP and a single pack of platelets. Similar recording of crystalloid volume and colloid volume of the initial 24 hours following admission will be undertaken. 8) Acute Hemolytic Transfusion Reactions: We will compare the incidence AHTRs (CDC NHSN Hemovigilance Surveillance definition) and will measure arrival serum haptoglobin levels. 9) Length of hospital and intensive care unit (ICU) stay: Length of stay will be determined from the date of admission for all enrolled patients.

Mechanistic Outcomes: The principle factors that may be responsible for beneficial clinical outcome effects associated with or attributable to LTLR-WB resuscitation when initiated early in the prehospital phase of injury are an important and essential objective of the proposed pilot trial. We will compare across treatment arms: 1) Coagulopathy: Coagulopathy will be assessed via PT/PTT/INR and rapid Thromboelastography (r-TEG) measurements. 2) Platelet Function: We will assess platelet activation, aggregation, and adhesion via flow cytometry analysis, whole blood aggregometry measurements and flow chamber analysis under shear stress conditions, respectively in a subset of patients.[88,89] 3) Glycocalyx integrity: We will assess glycocalyx integrity by measuring serum concentrations of Syndecan-1 and Hyaluronan by ELISA at in-hospital time points. 3) Donor Exposure, Age and Volume of Transfusion Products: During the prehospital and in-hospital acute resuscitation phase of the study the number donors from all transfused products blood products, the age of all LTLR-WB and PRBCs from the standard of care arm and overall transfusion volumes will be recorded and compared.

Blood Sampling and In-Hospital Measurements: In-hospital phase blood sampling will occur upon arrival (+ 4 hrs) and at 12 hours (+/- 12hrs) and 24 hours (+/- 12hrs) from time of arrival. Timing of samples will need to be flexible based upon patient availability and logistic factors. This early in-hospital sampling will allow adequate assessment of the benefits of early LTLR-WB resuscitation and appropriate characterization of the proposed clinical and mechanistic outcomes. TEG analysis at arrival, 12hr and 24hr time points will be performed on a TEG® 5000 Thromboelastograph® Hemostasis Analyzer.

2.9 STATISTICAL ANALYSIS

The overarching goals for the pilot trial are to evaluate safety, efficacy and feasibility of a LTLR-WB prehospital through in-hospital protocol to plan for the successful execution of a large, multicenter clinical trial. All analyses will be performed based on the intent-to-treat principle for the prehospital randomization and analyses will include all enrolled patients grouped by randomization assignment. This pilot study will guide the calculation needed for the large, multi-center clinical trial and will provide estimation for intra-cluster correlation coefficient and sample size variation across clusters. We will report 95% confidence intervals for all measurements

Safety and Efficacy Analysis: 28-day mortality is the primary safety and efficacy outcome and will be compared across randomized groups. Utilizing intention to treat principles we will compare the LTLR-WB and Standard of Care arms using a pooled Z test for comparing two independent proportions. We will additionally perform survival analysis for all mortality outcomes including 3hr, 6hr, 24hr, and 28day time points across the two arms of the study testing the differences using log rank test.

Eligibility, Enrollment, and Subject Accrual Anlaysis: The feasibility of enrollment will be evaluated by determining 1) the number of patients that meet the eligibility criteria for the trial; 2) the proportion of eligible patients that can be randomized and 3) the proportion of eligible patients who are enrolled in the trial. These proportions will be estimated directly as the observed ratio of numbers of patients, and 95% confidence intervals will be calculated to understand the likely range of values for a larger study with a comparable research protocol. The reasons why patients are not enrolled including frequencies of individual exclusions and the proportion of patients declining participation or not able to be randomized will be described. Rate of subjects' accrual per month with 95% C.I. will be calculated.

Adherence and Minimization of Bias: Adherence rates for each treatment arm of the protocol will be ascertained as the proportion of enrolled patients who adhere to the intervention (LTLR-WB vs. standard care) as assigned. Estimated proportions and 95% confidence intervals will be created. The trial has been designed to negate intervention arm crossover and maximize follow-up completion.

Estimates for Trial Secondary Clinical Outcomes: We will estimate the mean differences in the average Denver post-injury MOF score derived from the 3 highest daily scores between two treatment groups as the main clinical outcome for the pilot trial. We will also record and compare the overall proportion of patients who developed MOF based on Denver score > 3 and compare MOF free days. Similarly, the incidence of ARDS, NI, mortality (6hr, 24hr and 28 day) and hemolytic transfusion reactions will be recorded. We will perform survival analysis for all mortality outcomes. Blood component and resuscitation volumes over the initial 24 hours, length of ICU stay, days on a ventilator, and total hospital stay will be also be determined. Estimated proportions and means and 95% confidence intervals will be created for each outcome using the data from the entire pilot trial (i.e. combining the data from the two assigned treatment arms). Absolute and relative differences for continuous levels and event rates by assigned treatment will be estimated and 95% confidence intervals will be calculated to identify potential treatment differences for safety and for study planning purposes. Subgroup analyses will be exploratory and be based on baseline factors specified prior to the initiation of the trial.

The Following Outcomes Will Be Recorded:

1. The average Denver post-injury MOF score derived from the 3 highest daily scores. Differences between these averages will be estimated across the study two arms.
2. Proportion of patients who developed MOF based on Denver score > 3 and compare MOF free days across the study two arms.
3. The incidence of ARDS, NI, mortality (6hr, 24hr and 28 day) and hemolytic transfusion reactions will be recorded and compared across the study two arms
4. Survival analysis in relation to all causes of death.
5. Blood component and resuscitation volumes over the initial 24 hours,
6. Length of ICU stay, days on a ventilator, and total hospital stay will be also be determined.

Statistical Distributions of Enrolled Sample of Patients: Descriptive statistics, including means, standard deviations, medians, interquartile ranges, minimums, maximums, and frequency distributions, will be examined for all relevant measures. Transformations of measures will be considered based on distribution diagnostics and outlier analyses. The baseline characteristics of the patients in the entire trial will be described and 95% confidence intervals will be calculated to identify potential differences in baseline characteristics.

1. Estimated proportions and means and 95% confidence intervals will be created for each outcome using the data from the entire pilot trial (i.e. combining the data from the two assigned treatment arms).
2. Absolute and relative differences for continuous levels and event rates by assigned treatment will be estimated and 95% confidence intervals will be calculated to identify potential treatment differences for safety and for study planning purposes. Subgroup analyses will be exploratory and be based on baseline factors specified prior to the initiation of the trial.
3. Descriptive statistics, including means, standard deviations, medians, interquartile ranges, minimums, maximums, and frequency distributions, will be examined for all relevant measures.

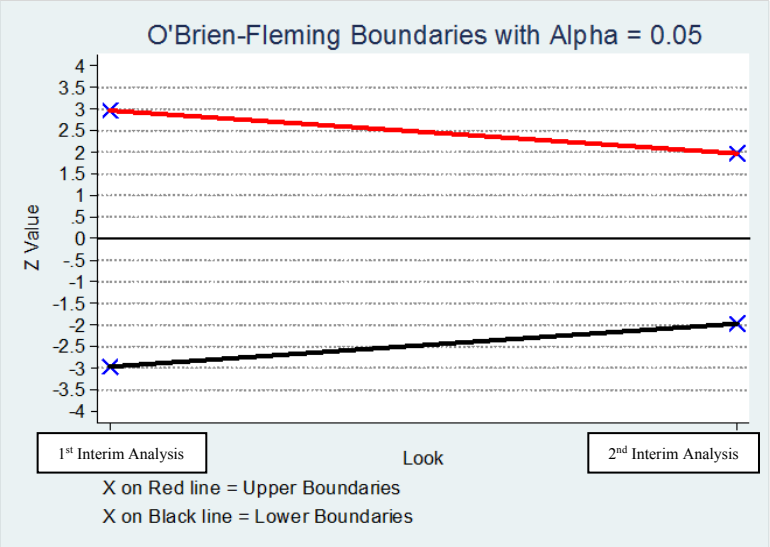
4. Transformations of measures will be considered based on distribution diagnostics and outlier analyses.
5. The baseline characteristics of the patients in the entire trial will be described and 95% confidence intervals will be calculated to identify potential differences in baseline characteristics.

Sample Size Justification for Pilot Trial: Assuming a baseline in-hospital mortality risk of 33% in the control arm as was demonstrated in the recently completed PAMPer trial with all cause in-hospital mortality as the primary outcome, enrolling **56 patients in each arm, 112 total patients** and using a 2 sided alpha of 0.05, the study will have a 80% power to detect a 22% (33% to 11%) or greater difference in in-hospital mortality. Based upon current PAMPer clinical outcome data and the additional benefit attributable to LTLR-WB when it is initiated in the prehospital setting, the current proposed mortality difference is clinically meaningful and of sufficient magnitude to influence clinical practice for a pilot trial. The above sample size will provide more than sufficient power for the originally planned feasibility outcomes as we have increased our sample size by 24%. The above power analysis was generated assuming 2 sequential tests using the O'Brien-Fleming spending function to determine test boundaries which are depicted in the following table and graph.

Details when Spending = O'Brien-Fleming, N1 = 56, N2 =56, P1 = 0.1100, P2 = 0.3300

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.50	-2.96259	2.96259	0.003051	0.003051	0.003051	0.164669	0.164669
2	1.00	-1.96857	1.96857	0.049002	0.046949	0.050000	0.636252	0.800921

Drift 2.81024



Based upon the busy air medical service at the University of Pittsburgh, the bases to be utilized for the pilot trial, 61 patients who met all inclusion and exclusion criteria for the current proposed pilot trial, were admitted to Presbyterian Hospital, consented and were enrolled (www.pamperstudy.com) over a 12 month period 6/2015-5/2016. Based upon a planned enrollment period of 2.5 years, this sample size is feasible after accounting for consent rates and exclusions.

3. HUMAN SUBJECTS

3.1 SUBJECT POPULATION

The study population will consist of injured patients at risk of hemorrhage being transported via air medical services from the scene of injury or from referring hospital to a definitive care trauma center participating in the PPOWER pilot trial. Patients will be enrolled in the prehospital setting prior to trauma center arrival with continuation of LTLR-WB resuscitation or standard of care resuscitation during the in-hospital acute resuscitation phase of the study

3.2 INCLUSION CRITERIA

1. Injured patients at the risk of Hemorrhage being transported from scene or referral hospital to a participating PPOWER trial site

AND

2A. Systolic blood pressure ≤ 90 mmHg AND tachycardia > 108 bpm at scene, or at outside hospital or during transport.

OR

2B. Systolic blood pressure ≤70 mmHg without tachycardia requirement, at scene or outside hospital or during transport.

3.3 EXCLUSION CRITERIA

1. Documented age: Age ≥90 or <18 years of age
2. Inability to obtain intravenous or interosseous access
3. Isolated fall from standing injury mechanism
4. Known prisoner or known pregnancy
5. Traumatic arrest with > 5 minutes of CPR without return of vital signs
6. Brain matter exposed or penetrating brain injury (GSW)
7. Isolated drowning or hanging victims
8. Isolated burns without evidence of traumatic injury
9. Referral Hospital In-patient admission
10. Objection to study voiced by subject or family member at scene
11. Wearing PPOWER opt-out bracelet

Inclusion and exclusion criteria will be assessed based on available information at the time of enrollment. Although all reasonable efforts will be made by the air medical crew to either directly witness or obtain documentation of eligibility criteria, due to the nature of the emergency pre-hospital setting, there may be occasions where the air medical crew must rely on verbal report of inclusion criteria, including qualifying vitals, from the referring hospital or ground crew. In these instances, if, after subsequent review of outside hospital and/or ground crew documentation, it is determined that the subject did not meet inclusion criteria and/or met exclusion criteria, the subject will remain enrolled in the study based on the intention-to-treat principle.

In the event that a verbal report must be used in lieu of physical documentation or directly witnessing the qualifying vitals, documentation of the verbal report will serve as the source documentation for determining eligibility. Verbal reports will be documented in the air medical record and will detail the information reported and by whom.

4. IRB APPROVAL AND FDA AMENDMENTS

The Investigator will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation. The Investigator should also notify the sponsor of this event.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Investigator's decision to modify the previously accepted clinical protocol, a Protocol Amendment will be submitted to the IND file for FDA review and comment prospective of implementation of the changes, as required. Changes that require prospective submission include:

- Any significant change in the design of the protocol (such as the addition or deletion of a control group).

The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

5. RECRUITMENT AND INFORMED CONSENT PROCEDURES

5.1 RECRUITMENT METHODS:

Subjects will be enrolled under "Exception from Informed Consent for emergency situations."

Subjects will be identified by prehospital air medical personnel at the scene, in transit or when being picked up from a referring facility. Subjects not enrolled by prehospital personnel but who meet all inclusion and no exclusion criteria may be identified and enrolled by research personnel after arrival to the ED and will be analyzed based on the arm assignment from which they originated per the intention to treat analytic plan.

In cases where the subject is incapacitated and unable to provide direct consent and an appropriate LAR is not present in the hospital, the consent will be obtained by phone/fax or electronically. The study will be discussed with the LAR over the telephone. If the LAR agrees, the consent form (ICF) will be sent electronically (email, fax, DocuSign, etc.) to the LAR. The investigator will go over the ICF with the Legally Authorized Representative. If the LAR agrees to participate in the research, the LAR will sign the ICF and send back to the Principal investigator electronically. An electronic picture of the signed signature page.forwarded to the consenting Investigator, will be accepted. The consent form may also be sent to the LAR via DocuSign, where the document can be reviewed in detail and digitally signed.

We will also send a postage paid envelope to the LAR for returning of the original complete signed informed consent whenever consent is obtained via email or fax.

If initial consent is obtained via LAR, the study team will routinely monitor the subject for capacity to consent while still admitted to the hospital. If it is determined by the Investigator, in conjunction with the assessment of the clinical team, that the subject has regained capacity, the Investigator will conduct the inform consent discussion and attempt to obtain continuing consent.

5.2 INFORMED CONSENT PROCEDURES

We anticipate that the pilot study will be conducted under the auspices and requirements of *exception from informed consent for planned emergency research* with regulatory oversight by the Food and Drug Administration (FDA) and Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24). This entails obtainment of an Investigational New Drug (IND) approval from the FDA, local IRB approval, community consultation, public notification, as well as notification of patients or their legally-authorized representative as soon as feasible after enrollment. Per regulation, we will attempt to obtain prospective informed consent from the subject or an appropriate LAR whenever feasible). However, we anticipate that prospective informed consent will not be feasible for the majority, if not all, of subjects enrolled. The patient and/or family member or LAR will be informed at the earliest feasible opportunity of the subject's inclusion in the clinical trial, and the details of the trial. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review if requested. The investigators will utilize available information and resources, such as social workers or social work notes, to try to locate the patient's legally authorized representative. If that search is unsuccessful, a notification letter will be sent to the subject's authorized representative explaining the study and providing contact information for answering questions. The letter will be sent via registered mail or by UPS and documentation of the addressee and date of mailing will be kept. If the subject becomes competent during the study period then he/she will be approached by a study Investigator for notification of enrollment and a similar provision of an opportunity to opt out from ongoing participation at the earliest opportunity. At any circumstance a subject or their legally authorized representative will have an opportunity to opt out of ongoing participation without penalty or loss of benefits. If the subject dies before consenting, a letter notification will be sent to the subject's family member to inform them that the subject was enrolled in this study**.**

Community consultation as outlined by the local IRB will be undertaken prior to IRB approval. Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. Bracelets will be made available that could be worn by members of the community who do not want to participate. Public notification and community consultation will be performed as directed by the local IRB and may include such methods as using random digit dialing telephone surveys of the proposed study community, targeted small group meetings, newspaper adds, bus add, social media, or consultation with community leaders. Due to ongoing participation and coordination of multiple large multicenter studies of this type, our institution has significant experience with community consultation and notification practices. Our community consultation plan is attached as an appendix **(Appendix 3)**

The following document describes the ***PPOWER study*** plan for Waiver of Consent for Planned Emergency Research in compliance with 21 CFR 50.24. We are requesting this waiver because these human subjects are in a life-threatening situation, current available treatment is unsatisfactory, and it is necessary to determine the safety and effectiveness of whole blood transfusion in the prehospital setting. Obtaining informed consent is not feasible because the

subjects will be unable to provide consent due to their medical condition and the intervention will need to be administered before consent from a legally authorized representative is feasible.
Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

6. POTENTIAL RISKS AND BENEFITS

6.1 POTENTIAL RISKS

Risks Associated With LTLR-WB: The whole blood product to be utilized starting in the prehospital environment in the pilot clinical trial is the identical product to be used in the hospital and identical to the current whole blood product that has been transfused in over 200 patients over the last 24 months at the University of Pittsburgh without evidence of complications or transfusion reactions. The primary risk with LTLR-WB is a hemolytic transfusion reaction which will be followed as an important secondary outcome. There have been no hemolytic transfusion reactions in over 200 patients transfused LTLR-WB at the University of Pittsburgh in the last 24 months. The primary risks with any blood transfusion can be found in the Circular of Information prepared jointly by AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program. Those primary acute immunologic complications include hemolytic transfusion reactions, immune mediated platelet destruction, febrile nonhemolytic reactions, allergic reactions, anaphylactoid reactions and transfusion-related acute lung injury (TRALI). Delayed immunologic complications include delayed hemolytic reaction, alloimmunization, posttransfusion purpura, transfusion-associated graft-vs-host disease. Nonimmunologic complications include transmission of infectious agents, bacterial sepsis, transfusion-associated circulatory overload (TACO), hypothermia and metabolic complications.

The primary risk associated with transfusion of Rh+ blood into a woman of child-bearing potential (WCP) is hemolytic disease of the fetus and newborn (HDFN) of a future pregnancy. Complications of HDFN include fetal anemia, fetal hydrops, and in the most severe cases, fetal death. However, the overall risk of poor fetal outcome in a future pregnancy for Rh- women that are administered Rh+ blood products has been estimated to be less than 0.5%[90]. Of note, the incidence of a female being Rh- is only 15%. This means that the majority of WCP are at no risk of Rh mismatch. For those WCP that are at risk, the likelihood of poor fetal outcome is very small.

6.1.2 Risk of Study Procedures

Risk of breach of confidentiality: When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identities. The PI and other study personnel will ensure that the subject's confidentiality will be maintained. Subject name and other identifiable information will be kept in a secure, locked, limited access area such as a password protected database. Subjects will be provided a unique study identification number.

Risk of venipuncture: Any labs drawn for research will try to be coordinated with labs being drawn for conventional care. Any venipuncture performed will be done so using aseptic technique by a clinical team member trained in phlebotomy.

6.2 ALTERNATIVE TREATMENTS

Prehospital air medical standard of care resuscitation and in-hospital standard of care resuscitation will be employed.

6.3 POTENTIAL BENEFITS

We anticipate that the benefits of getting whole blood may reduce bleeding in some patients, and possibly reduce overall blood transfusion requirements during the first day after injury. Prior studies have suggested that early whole blood transfusion may improve outcomes in patients with a lot of blood loss. Whether the subject receives the early whole blood transfusion, s/he may also benefit from increased observation at the time points involved in the study. Ultimately subject participation may help us to improve prehospital treatment of trauma injuries.

6.4 DATA SAFETY MONITORING

6.4.1 Data Safety Monitoring Board

The Clinical Coordinating Center will be led by Dr. Sperry (PI) for the pilot trial with the assistance of MACRO and associated clinical research infrastructure at the University of Pittsburgh. Given the small size and resources allotted for the pilot trial, we will not have a formal Data Coordinating Center and the data coordination will be performed by the Clinical Coordinating Center. A Steering Committee chaired by Dr. Triulzi (Co-PI) will be charged with overseeing the study and make all major organizational and policy decisions. Committee members will include Dr. Sperry, Dr. Guyette and Dr. Zuckerbraun. This group will have conference calls as needed for smooth execution of the trial. Members of a Data Safety Monitoring Board (DSMB) will be appointed and will include experts in *hematology, surgery (trauma/critical medicine), bioethics, and biostatistics*. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

Any perceived or real conflicts of interest will be submitted to the University of Pittsburgh Conflict of Interest office. If required, a management plan will be instituted to manage the conflict of interest. At this time, no one on the study team has a conflict of interest.

6.4.2 Data Safety Monitoring Plan

The proposed study will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any fatal or life threatening AE, which is unexpected and related or possibly related to study intervention, will be reported immediately to the IRB and may be followed by an additional letter detailing the nature of the SAE if needed. In the event that a participant either withdraws from the study or the investigators decide to discontinue a participant due to a SAE, the participant will be monitored by the co-PIs until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Outcomes of related or possibly related SAEs will be regularly reported to the IRB, DSMB, and the sponsor. A summary of the SAEs that occurred during the previous year will be included in the annual progress report as well as in the annual IRB renewal.

Our DSMB responsibilities are listed as an appendix **(Appendix 2).** The DSMB will monitor accruing data in order to confirm patient safety throughout the trial. All study personnel will be trained on the protection of human subjects. Although the DSMB will make the final decision about the monitoring plan, we anticipate that the DSMB will evaluate the rate of adverse events between the treatment and control arms every 6 months during enrollment. The DSMB will also monitor primary, secondary study outcomes between the treatment and control groups including

main effects and a priori subgroups as specified elsewhere in the protocol. The DSMB will advise the investigators if a change in the protocol is warranted based on this monitoring.
The Medical Monitor is required to review all unexpected serious adverse events and other unanticipated problems involving risk to subjects or others. At a minimum, the medical monitor must comment on the outcomes of the event or problem and, in case of a serious adverse event, comment on the relationship to participation in the study. The Medical Monitor may review unblinded data in order to assist with his review.

Study Changes

If the PI and study team plan to modify the study, they will submit the amendment to the University of Pittsburgh HRPO along with all study documents to be changed (i.e. protocol, consent form, etc.) Once IRB approval is obtained, the study team will submit the changes to the NIH at the next reporting cycle unless earlier notification is warranted. If it is a significant change, the PI will request approval by the NIH Program Officer and DSMB prior to modification. Any changes will also be reviewed by the Office for Investigator-Sponsored IND and IDE Support (O3IS) for determination if the change requires prospective FDA review or if it can be submitted at annual report.

Data Analysis Plan Overall guideline:

1. Nature of this study: Pilot study
2. Overall objectives: Evaluate safety, efficacy, and feasibility of a LTLR-WB prehospital thru in-hospital protocol. The study will provide estimation for intra-cluster correlation coefficient and sample size variation across clusters for the design for a future full scope large clinical trail
3. ***Analysis Principle: Intent-to-treat for the prehospital randomization assignment. 95% confidence intervals for all measurements***

Safety and Efficacy Analysis:

1. In-hospital mortality is the primary safety and efficacy outcome and will be compared across randomized groups.
2. LTLR-WB and Standard of Care arms will be compared using a pooled Z test of two independent proportions.
3. Survival analysis will be conducting looking at median survival at 3hr, 6hr, 24hr, and 28day time points across the two arms of the study testing the differences using log rank test.

Eligibility, Enrollment, and Subject Accrual:

The feasibility of enrollment will be evaluated by determining, ratio of the following parameters will be calculated along with 95% confidence intervals:

1) the number of patients that meet the eligibility criteria for the trial;
2) the proportion of eligible patients that can be randomized and
3) the proportion of eligible patients who are enrolled in the trial.

Additionally:

1. The reasons of not enrollment will be recorded with related frequency and percentages.

2. Frequency of patients eligible but not enrolled will be recorded
3. Frequency of patients randomized but not included in the study will be recorded
4. Rate of subjects' accrual per month with 95% C.I. will be calculated.
5. Adherence rates for each treatment arm of the protocol will be ascertained and recorded as the proportion of enrolled patient who adhere to each of the study arms

Interim Analysis

The main points in the interim analysis:

1. Monitor the eligibility, enrollment, and subject accrual as stated above.
2. Safety and efficacy by looking for In-hospital mortality differences between LTLR-WB and Standard of Care arms and compared these ratios using a pooled Z test of two independent proportions. Stopping rules will be used in the study interim analysis.
3. Survival analysis will be monitored in the interim analysis
4. Secondary outcomes will be checked and related 95% C.I will be estimated across the study two arms.
5. Unanticipated Events
6. Protocol deviation

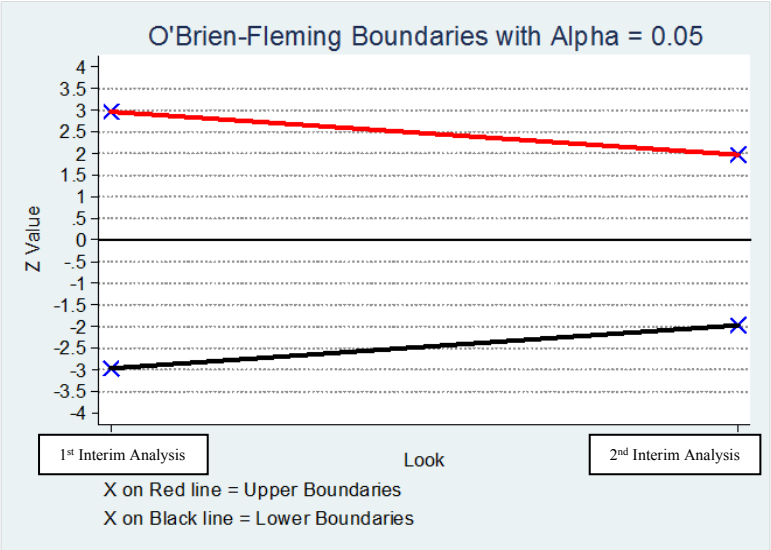
Stopping rules

The following stopping rules of O'brien-Fleming boundaries will be implemented in the interim analysis:

Details when Spending = O'Brien-Fleming, N1 = 56, N2 =56, P1 = 0.1100, P2 = 0.3300

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.50	-2.96259	2.96259	0.003051	0.003051	0.003051	0.164669	0.164669
2	1.00	-1.96857	1.96857	0.049002	0.046949	0.050000	0.636252	0.800921

Drift2.81024



6.4.3 Parameters to be Monitored by Local Study Team

The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

- An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.
- A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.
- An assessment of external factors or relevant information (eg. pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.
- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

Summary of Reports

A summary of the data and safety monitoring meetings will be reported to the University of Pittsburgh HRPO office during annual renewal and to the NIH as required. The DSMB chair and NIH Program Officer will regularly receive reports of enrollment, demographics, AE/SAEs, and UAPs. Annual IND reports will be submitted to the FDA via the University of Pittsburgh's O3IS (Investigator-Sponsored IND and IDE Support Office).

6.4.4 Frequency of Monitoring

The Investigator will review subject safety data as it is generated. The Investigator, sub-investigators, and the research staff will meet on at least a quarterly interval during the active recruitment phase of the study to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints and confidentiality of subjects. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

6.4.5 Reportable Adverse Events

Assessing and Reporting Adverse Events (AEs): Enrolled subjects will be monitored for adverse events throughout the first 48 hours after hospital admission. Reporting forms will be submitted to the DSMB and IRB. Potential adverse events occurring within the first 48 hours after admission will be reviewed as to treatment arm and further classified by: a) Severity (life-threatening, serious, non-serious); b) Expected vs. Unexpected; and c) Related, Possibly Related, Probably Not Related, or Definitely Not Related. For serious adverse events that are related or possibly related to the study or intervention, the coordinating center will notify the IRB and the DSMB as well as additional appropriate regulatory agencies and sponsor promptly. The coordinating center will tabulate and report compliance, data quality, and non-serious adverse events on a regular basis.

Expected adverse events are commonly observed in patients who are at risk of hemorrhage following traumatic injury and may or may not be attributable to the LTLR-WB. Clinical diagnoses of pneumonia, sepsis, cerebral bleeding, stroke, seizures, surgical interventions, complications due to specific injuries as well as other major medical or surgical complications are commonly

observed in these patients. They will be recorded as noted in the hospital discharge summary as complications and will not be reported as adverse events.

6.4.6 Adverse Events Reporting Timeline

A table summarizing reporting timelines is provided below:

Organization	Fatal/Life Threatening SUSAR	Non-fatal, non-life threatening SUSAR	SAE (expected and related)	UP (not involving risk)	UPIRTSO
IRB	24 hours	10 working days	No requirement	No reporting**	10 working days
FDA	7 calendar days	15 calendar days	No requirement	No requirement	14 days*
NHLBI	7 calendar days	7 calendar days	No requirement	No requirement	14 days*
Medical Monitor	24 hours	7 calendar days	No reporting	No reporting	14 days*
DSMB	24 hours	7 calendar days	At next meeting (every 6 months)	At next meeting (every 6 months)	14 days*

*Reporting occurs only after an IRB determination of UPIRTSO has been received
**No direct reporting is required; events are documented on a log that can be reviewed upon request

Prehospital Transfusion Adverse Events/Look Back Standard Operating Procedure (SOP):

a. Transfusion rate will be compatible with the patient's condition. The patient will be monitored closely during the entire transfusion. The documented start and stop times are directly related to the actual transfusion of the component. Study coordinators will assume responsibility of additional vital signs and completion of the whole blood

b. The patient medical record shall include the following:

1. Name of the components transfused
2. Donation identification number
3. Date and time of transfusion (Start and Stop time)
4. Pre and post transfusion vital signs
5. The volume or # of units transfused
6. The transfusionist's name (paramedic)
7. Documentation of related adverse events

c. Procedure for transfusion reactions:

This is modified from UPMC policy for Blood Transfusions to be applicable for this study.

1. Careful observation throughout the transfusion allows for early detection of adverse reactions and optimal treatment, if necessary. All reactions should be handled initially as possible hemolytic reactions and the transfusion must be stopped. Any adverse events associated with the transfusion of blood or blood components should be documented in the patient's Medical Record and reported to the blood bank/ transfusion service. Prehospital providers initiating transfusion of blood products will monitor vitals

throughout transport. If clinical concern for a transfusion reaction occurs, the transfusion will be stopped, and supportive care will continue. The concern for a transfusion reaction will then be communicated to the trauma center staff.

2. The most common clinical events accompanying or announcing transfusion reactions are, in order of decreasing frequency:

a. Fever, with or without chills
b. Skin symptoms, hives and/or itching or rash
c. Chest pain
d. Hypotension
e. Nausea
f. Flushing
g. Respiratory Distress (wheezing, coughing or dyspnea)
h. Bleeding at infusion site
i. Hemoglobinuria
j. Circulatory overload
k. Anaphylaxis

3. If an adverse reaction is suspected, the procedure below will be followed:

a. Stop the transfusion
b. Maintain IV access with Normal Saline and change the tubing.
c. Notify the patient's physician upon arrival to the ED and initiate immediate treatment as ordered.

4. For all other blood products involved in a reaction, all blood products shall be stopped and a transfusion reaction investigation shall be initiated per standard blood bank guidelines

5. Notify the Blood Bank of the suspected transfusion reaction.

6. Collect a sample drawn from the patient as soon after the reaction was detected. Send a 6 mls pink top tube, labeled with a new Blood Bank armband to the Blood Bank along with the unused blood, blood bag with attached hard back copy of the transfusion tag, the IV tubing used and the top 2 copies of the Transfusion Reaction Investigation 3 part form. The back copy of the Transfusion Reaction Investigation form should remain in the patient's chart as the initial report. A post transfusion reaction Urinalysis with Microscopic may also be ordered by the patient's physician.

7. The Blood Bank will complete the Transfusion Reaction initial report and notify the caregiver of the critical results. Pathology will evaluate the patient's reactions, Blood Bank's initial report, culture when indicated, and report will be documented in the patient's medical record. Consultation between the Medical Director of the Transfusion Service, the patient's physician and Risk Management is required when a fatal hemolytic transfusion reaction occurs. Further evaluation and FDA notification may be indicated. The participating centers Transfusion Service is responsible for peer review and blood utilization practice.

8. Look back procedures: Since the plasma will be tracked through the participating centers Blood Bank/Transfusion service look back/product recall procedures will be conducted as per standard protocol (**Appendix 6**).

6.4.7 Withdrawal of Subjects and Stopping Criteria:

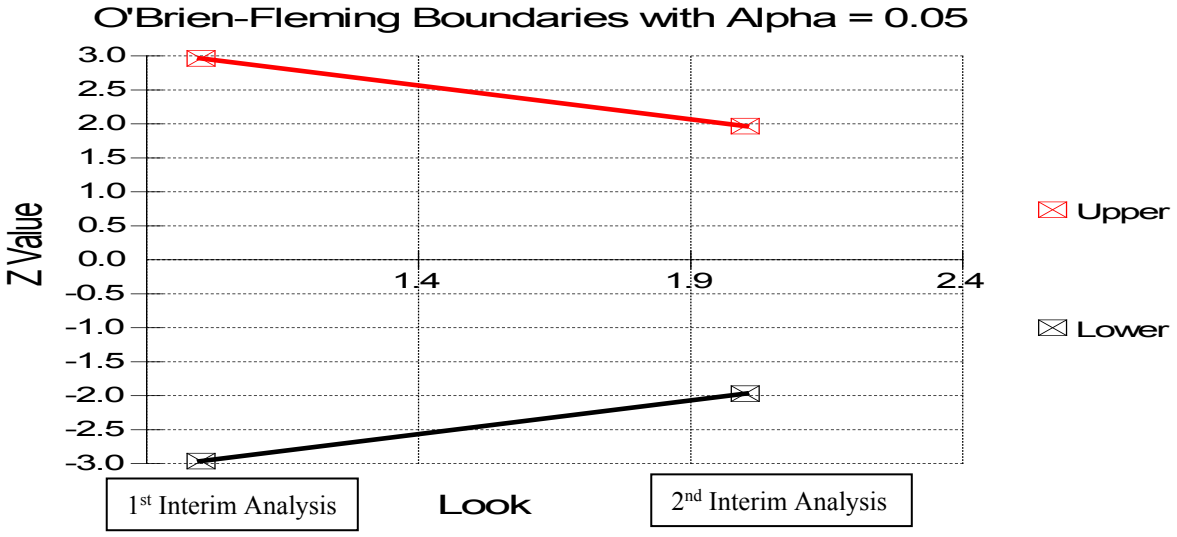
Assuming a baseline in-hospital mortality risk of 33% in the control arm as was demonstrated in the recently completed PAMPer trial (manuscript in preparation) with all cause in-hospital mortality as the primary outcome, enrolling **56 patients in each arm, 112 total patients** and using a 2 sided alpha of 0.05, the study will have a 80% power to detect a 22% (33% to 11%) or greater difference in in-hospital mortality. Based upon current PAMPer clinical

outcome data and the additional benefit attributable to LTLR-WB when it is initiated in the prehospital setting, the current proposed mortality difference is clinically meaningful and of sufficient magnitude to influence clinical practice for a pilot trial. The above sample size will provide more than sufficient power for the originally planned feasibility outcomes as we have increased our sample size by 24%. The above power analysis was generated assuming 2 sequential test are made using the O'Brien-Fleming spending function to determine test boundaries which are depicted in the following table and graph.

Details when Spending = O'Brien-Fleming, N1 = 56, N2 =56, P1 = 0.1100, P2 = 0.3300

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.50	-2.96259	2.96259	0.003051	0.003051	0.003051	0.164669	0.164669
2	1.00	-1.96857	1.96857	0.049002	0.046949	0.050000	0.636252	0.800921

Drift 2.81024



Discontinuation of the Clinical Trial:

The investigator may withdraw a subject from participating in this research if circumstances arise which warrant doing so. The decision may be made either to protect the subject's health and safety, or because the subject's condition did not meet certain criteria needed for study inclusion.

6.5 RISKS MANAGEMENT PROCEDURES

6.5.1 Protection Against Risks

General Risks of Study Protocol and Procedures

Data collected will include a review of the air medical patient care report(s), Emergency Department and electronic/ paper hospital records. Prehospital Data**:** Demographics, air medical response times (call receipt to arrival, arrival at patient side,) injury characteristics, vital signs, prehospital resuscitation volumes, prehospital interventions (needle decompression, chest tubes)

referring hospital vitals, and interventions will be recorded. In-Hospital Data: Demographics, shock severity (base deficit, lactate), injury characteristics, ED vitals, ED interventions (chest tubes, intubation), injury severity, operative interventions and timing of interventions, injury severity score, ICU days, ventilator days, length of stay, multiple organ dysfunction scores (daily), nosocomial infectious outcomes, blood gas results, chest x-ray reads, transfusion of blood and blood components, resuscitation requirements, all primary and secondary outcomes will be recorded.

Data Entry and Storage: MACRO and associated internet technology affiliates at the University of Pittsburgh will create web-based data entry platform to collect necessary information for the proposed pilot study.

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

A Case Report Form will be completed for each subject enrolled into the clinical study. The Investigator will attest that all clinical and laboratory data entered on the CRF are complete, accurate and authentic using a signoff page within the data entry platform. A key linking the subject to the code number will be kept locked in a secure location and will be available only to the investigators. The data and samples will be retained indefinitely and used for future testing. Data from this study, without the subject's identity, may be reported in scientific meetings, articles or other appropriate communications.

The Investigator will retain the data for the entire period of this study and will retain the specified records and reports for a minimum of 7 years after completion of the study. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

6.5.2 Protection Against Potential Risks of Experimental Intervention

MACRO research coordinators for the pilot trial will document and verify all trauma arrivals via air medical transport for PPOWER enrollment. Those patients who met inclusion and exclusion criteria during air medical transport that were enrolled will be verified and those patients will undergo initial laboratory and blood sampling within the first hour of arrival. All requirements for notification for *exception from informed consent for emergency research and Title 21, Code of Federal Regulations, Section 50.24 (21 CFR 50.24)* will be explicitly followed **(Appendix 4)**.

Training and Participating Site Coordination: As the clinical coordinating center for the proposed pilot trial the University of Pittsburgh will be responsible for all research coordinator training, prehospital provider training and sample collection and storage. Research coordinators, prehospital providers and associated staff will be trained during the months prior to the trial start date regarding the scientific basis for the study, specific inclusion and exclusion criteria, sample collection and processing, prehospital procedures and SOPs, and rapid TEG performance. Trial enrollment and maintenance of data integrity will be assessed monthly using the web-based data platform. Trial screening, enrollment and data completeness and accuracy will be accessed at regular intervals via random patient audit.

7. COSTS AND PAYMENTS

Neither the participant, nor the insurance provider will be charged for the costs performed only for the purposes of this research study. Subject will be charged in the usual

manner for any procedures performed as part of your standard medical care (care the subject would receive even if they were not participating in this research study).

8. QUALIFICATIONS AND SOURCE OF SUPPORT

8.1 QUALIFICATIONS OF THE INVESTIGATORS

Jason Sperry, MD MPH is a Professor of Surgery and Critical Care Medicine at the University of Pittsburgh and the PI for the ongoing DoD funded PAMPer and STAAMP multicenter, randomized, clinical trials which investigate prehospital plasma and tranexamic acid in the prehospital setting during air medical transport. Dr. Sperry is an authority on interventional clinical trials in the prehospital setting, coagulopathy, massive transfusion and clinical outcomes research and comparative effectiveness studies following traumatic injury. He is an executive board member of MACRO, the interdepartmental Multidisciplinary Acute Care Research Organization which will provide the clinical coordination for the LITES network. He is also a Co-investigator for NHLBI funded TACTIC and is the Chair of the multicenter trials committee for the American Association for the Surgery of Trauma (AAST) and on the executive committee for the National Trauma Research Repository (NTRR) under the direction of the National Trauma Institute (NTI).

Frank Guyette MD, MPH is an Associate Professor of Emergency Medicine and is the Co-PI for the ongoing DoD funded PAMPer and STAAMP trials at the University of Pittsburgh. Dr. Guyette is a ROC investigator and was the PI of the ROC (Biomarker Lactate for the Assessment of Trauma) BLAST study. He is board certified in EM and EMS and is the Medical Director for STAT MedEvac, the nation's largest non-profit critical care transport group. His leadership roles in the EMS community include Chair of the Pennsylvania Chapter American College of Emergency Medicine (PACEP) EMS Committee, National Association of EMS physician (NAEMSP) Air Medical Committee, and the American College of Emergency Physician member of the board of directors of the Commission on Accreditation of Medical Transport Systems (CAMTS). Dr. Guyette also serves as a member of the EMS COMPASS Evidence Review Group participating in the development of evidence based prehospital performance measures. His area of expertise is prehospital clinical outcomes research with a focus and multiple publications on out of hospital critical illness, prehospital resuscitation, prehospital point of care testing, and emergency medical service education.

Matthew Neal, MD is an Assistant Professor of Surgery at the University of Pittsburgh. His lab focuses on the mechanisms of organ failure and coagulopathy following trauma and hemorrhage. Specifically, he is interested in the role of innate immune activation in the regulation of hemostasis and thrombosis. He is particularly interested in platelet biology in sterile injury and sepsis. In addition, he has a translational research interest in outcomes following massive transfusion and the clinical assessment of coagulation defects in trauma and sepsis.

Darrell J. Triulzi, MD is a Professor of Pathology and Medicine, University of Pittsburgh, with subspecialty training and board certification in Transfusion Medicine/ Blood Banking. He has been director of the Division of Transfusion Medicine at UPMC hospitals since 1991. He has participated as both PI and co-investigator in federally funded clinical studies in transfusion medicine and has numerous publications in the field. He is also Medical Director of the Institute for Transfusion Medicine, which provides transfusion support to UPMC hospitals through Central Blood Bank.

Mazen Zenati, MD, PhD is an Assistant Professor at University of Pittsburgh. Dr. Zenati will assist with statistical analysis for this study.

Mark Yazer, MD is a board-certified expert in transfusion medicine and full-time faculty at UPMC Department of Pathology. Dr. Yazer is an experienced clinical trialist and has participated in other NIH funded clinical trials.

8.2 SOURCES OF SUPPORT

Cold stored, low titer, platelet replete-leukocyte reduced, group O whole blood (LTLR WB), Federal Sponsor: National Institutes of Health Grant number 1R34HL135224-01A1

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Clinical Protocol Appendix 1 Blood Product Maintenance

CENTER FOR EMERGENCY MEDICINE OF WESTERN PENNSYLVANIA, INC. STAT MEDEVAC

Blood Product Maintenance Policy:

1. Base site blood products will be inspected daily for adequate temperature maintenance in the blood product storage refrigerator. Daily temperature checks will be documented in conjunction with the weekly circular graph temperature recording. Blood products will also be properly signed out of the blood refrigerator when indicated for missions and maintained at proper temperature until transfused or returned to the refrigerator.
2. Inventory/Expiration Tracking Log
   a. All PRBC units must be logged on this sheet when received from the designated distribution point:
      1. STAT MedEvac 1 – Washington Hospital Transfusion Services Lab
      2. STAT MedEvac 2 -Johnstown American Red Cross
      3. STAT MedEvac 3 – UPMC Passavant Cranberry Blood Bank
      4. STAT MedEvac 4 – UPMC McKeesport Transfusion Services Lab
      5. STAT MedEvac 5 – Uniontown Hospital Blood Bank
      6. STAT MedEvac 6 – Clarion Hospital Blood Bank
      7. STAT MedEvac 7 – UPMC Horizon Transfusion Services Lab
      8. STAT MedEvac 8 – UPMC Passavant Cranberry
      9. STAT MedEvac 9 – American Red Cross
      10. STAT MedEvac 10 – John Hopkins Hospital
      11. STAT MedEvac 11 -Altoona Hospital Blood Bank
      12. STAT MedEvac 13 – Baltimore American Red Cross
      13. STAT MedEvac 14 – UPMC Passavant Cranberry Blood Bank
      14. STAT MedEvac 15 – Washington Hospital Transfusion Services Lab
      15. STAT MedEvac 16 – UPMC Passavant Cranberry Blood Bank
      16. STAT MedEvac 17 – UPMC Hamot
      17. STAT MedEvac 18 – Children's National Medical Center Blood Bank
   b. Record the following information:

1. Unit Number
2. Date placed in service
3. Date unit will expire
4. Date unit is to be returned (minimum of 10 days prior to expiration date on blood products)
5. Initials of person confirming ABO type and placing units into service.
6. Disposition of units (transfused, wasted, or returned)
7. Location:- Note the receiving facility where patient receiving PRBCs transfusion was admitted.
8. Paperwork: Check that all appropriate paperwork is complet
   ed.
9. Comments: As needed, and list flight number associated with blood product transfusion.
10. Initials of person completing log regarding unit disposition.

3. Daily Checks / Shift Responsibilities: In order to prevent any problems with the recording chart to potentially go undetected for as long as 24 hours, check the chart midway through the shift for accurate documentation of current day and time every shift. Any problems should be corrected immediately and documented on the recording chart.
   a. Temperature and Visual Inspection to be completed on every shift recording the following information on the Temperature Check and Visual Inspection Sheet:
      1. Date of inspection
      2. Temperatures as indicated
         a. Make sure temperature reading on recording chart corresponds with current day, time.
         b. Make sure stylus is making contact with recording chart.
         c. Notify Base Site Manager of any problems, i.e.: possibility of contamination, temperature not maintained between 1o C to 6° C, inability to get recording chart to function properly.
      3. Refrigerator graph: Confirm accurate documentation of current day and time on the circular graph. Internal refrigerator temperatures and chart temperatures must both be within acceptable range (1-6° C) and agree with each other :t1°
         a. Any gaps or fluctuations in temperature on recording chart must have explanation documented on chart followed by your initials.
         b. A copy of all temperature documentation will be sent to the appropriate blood bank by the Base Site Coordinator or base representative.
      4. Contamination: Check each unit of blood for contamination and expiration date- i.e., if the red cell mass appears purple; if there is a zone of hemolysis: visible clots; if the plasma is murky; if plasma has a purple, brown, or red discoloration; if there are signs of leakage or inadequate sealing.
         a. PRBC units that are questionable must be

quarantined and recorded as such in the comments section.

b. Notify the appropriate blood bank immediately of quarantined blood.

c. Exchange quarantined units for replacement units as soon as possible.

5. Confirm that blood is "0" negative or positive.

6. Confirm that blood is not due to expire by checking the inventory and expiration tracking log. If blood is to be returned, follow blood product return/transfer procedure.

7. Confirm ice or commercial ice packs are available for transport.

8. Comments as needed

9. Initials of person doing inspection.

b. Ensure refrigerator is clean and in working order.

3. Visual Inspection: Check appearance for contamination, clots, discoloration, etc. List as satisfactory or unsatisfactory.

4. Initials: Your initials.

5. Comments: Insert flight number and patient name if blood product was transfused.

7. Packing blood products for a mission

a. Blood products are to be taken on every mission.

b. Each unit should be in the plastic blood product bags

c. Place in the insulated cooler with commercial ice packs or ice and an appropriate thermometer. The units should be "sandwiched" between the ice using appropriate barriers to prevent the units from coming in direct contact with the ice.

d. If blood is not transfused, return it to the blood product refrigerator upon returning to base. Fill out remaining Columns 6-10 of Blood Tracking Log

8. Administration of blood products is to be carried out in strict accordance with STAT MedEvac Critical Care Protocols.

9. Documentation of transfusion

a. When a unit is transfused during a mission make sure the appropriate information is relayed to the receiving facility including type and unit number.

b. Fill out appropriate blood bank forms for transfused products per Central Blood Bank / American Red Cross instructions.

c. Upon return to the base, fill out the Blood Tracking Log for Columns 6-10 as instructed.

10. Replacement of transfused blood products

a. Notify appropriate blood bank that you have transfused blood and specify the number of replacements needed.

i. Notify STAT Com and the Medical Director on call of any delay in receiving replacement units of blood and document the delay via special report.

11. Transfusion Complications

a. Notify the receiving facility of the patient's signs and symptoms immediately upon arrival.

b. Upon returning to base, an Adverse Reaction special report should be completed.

11. Blood refrigerator alarms

a. Monthly Check- High and low temperature alarms to be checked on the first of every month.

i. Remove blood from refrigerator and place on ice in cooler.

ii. Remove probe from glycerol solution and place the probe on ice. Temperature of probe will register below 1c C within several minutes to activate alarm.

iii. The designated operator should call to advise of the Alarm. Activate the silence button on the blood product storage refrigerator after receiving phone call.

iv. Then place probe in tepid water to test high temperature alarm (>6°).

v. Again, the designated operator should call to confirm alarm activation. Activate the silence button on the blood product storage refrigerator after receiving phone call.

vi. Initial and note "Alarm Test" on Temperature Graph.

vii. Document "Alarms Checked/Operational or Non-Operational" in comment section of Daily Temperature Checks and Visual Inspection Logs.

viii. If alarms fail or no phone call is received from the designated operator keep blood on ice in cooler and notify the Base Site Manager immediately for guidance.

c. Alarm Activation

i. The blood bank refrigerator will alarm any time the temperature in it rises above 6°C or below 1 0C or electrical power is shut *off* to the refrigerator.

ii. At the same time, the remote alarm will be activated at the Communications Specialist's switch board, the Communications Specialist will notify you by phone when the alarm activates.

iii. When alarm goes *off,* try to find any obvious causes, i.e., door is open to refrigerator, refrigerator is unplugged, circuit breaker is *off,* or circulating fan is not working.

iv. If cause cannot be found or corrected, removed blood and place it on ice in the cooler.

v. Notify the Base Site Manager immediately of problem. The Base Site Manager will instruct you as to what to do with the units of blood.

12. Quarterly Temperature Monitoring

a. Every quarter (March, June, September, and December) a verification of temperature maintenance of blood during emergency flights must be performed.

b. The following steps are to be performed when testing the temperatures:

1. Store the bottle in your refrigerator along with the units of blood until needed.
2. When packing units for an emergency, record the thermometer reading, time packed, date and initials on the card provided.
3. Place the bottle into the cooler along with the blood.
4. Assure that all the blood units and the bottle are covered with ice.

5. Upon return to base after flight, record the thermometer reading, time unpacked, date, and initials on the bottom of the card provided.
6. The acceptable range during transport is 1-10.

c. A record of all results will be maintained at the base

Appendix 2 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be created to review this study. After initial approval and at periodic intervals (to be determined by the committee) during the course of the study, the DSMB responsibilities are to:

1. ***Review the research protocol, informed consent documents and plans for data and safety monitoring;***
2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors that can affect study outcome;
3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
4. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the PI;
5. Protect the safety of the study participants;
6. Report on the safety and progress of the study;
7. Make recommendations to the PI, and if required, to the DoD or FDA concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;
8. Monitor the confidentiality of the study data and the results of monitoring;
9. Assist the PI by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will include experts in *hematology, surgery (trauma/critical medicine), bioethics, and biostatistics*. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

The University of Pittsburgh Office of Clinical Research, Health Sciences / CTSI will provide the logistical management and support of the DSMB. A safety officer (chairperson) will be identified at the first meeting. This person will be the contact person for serious adverse event reporting. Procedures for this will be discussed at the first meeting.

The first meeting will take place before initiation of the study to discuss the protocol, approve the commencement of the study, and to establish guidelines to monitor the study. The follow-up meeting frequency of the DSMB will be determined during the first meeting. An emergency meeting of the DSMB will be called at any time by the Chairperson should questions of patient safety arise.

Appendix 3 Community consultation plan draft

We will conduct public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

The following section describes our notification procedures:

- **Website**. The University of Pittsburgh has an already established web site – acutecareresearch.org-which was designed to maintain communication and provide updates about emergency studies. The website includes our phone numbers, and an email account for communication. The website also has a dialogue box allowing anonymous email communication for persons who do not wish to leave their names.
- **Bumper ads on mass transit**. These ads will be visible to the entire metropolitan area, and are constantly in motion. The ads will direct viewers to our website.
- **Flyers.** We will distribute flyers directing traffic to our local website. Flyers will be provided in hospital waiting areas and community bulletins boards.
- **Presentation to local paramedics, emergency physicians and medical directors.** We will create an email list-serve using Campaign Monitor. We will add any community members that express interest in our research based on emails, calls, inquiries or referrals.

Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.

The following section describes some of our consultation procedures:

- **Website**. The University of Pittsburgh has an already established web site – acutecareresearch.org-which was designed to maintain communication and provide updates about emergency studies. The website includes our phone numbers, and an email account for communication. The website also has a dialogue box allowing anonymous email communication for persons who do not wish to leave their names. Also, anyone wishing to "opt out" will be provided the lead coordinator's number to call and will be provided with a bracelet to wear indicating they do not wish to be part of the PPOWER study.
- **Feedback from community will be recorded.** Since the population eligible for enrollment includes all citizens in the study region it will not be possible to target any particular small group. Feedback from the community will be recorded by research personnel regarding any concerns they may have about potential enrollment.
- **Paper Surveys:** Paper surveys will be placed in the trauma clinic, around campus and in the Emergency Department. The questions will be similar to the telephone survey. We will tally the results and present them to the IRB at the time of their community consultation plan evaluation.

- **Presentation to Pennsylvania Emergency Health Services Counsel.** This group reviews research for the State Department of Health. We will schedule to present at one of their meetings, solicit and record their feedback, and present these findings to the IRB.
- **Telephone calls**. We will have the lead coordinator's telephone number on the website for interested parties to call. All calls will be returned, and "opt out" bracelets sent to any requesting them. Any voiced protestations will be recorded and presented to the IRB.
- **Telephone Survey.** A very detailed telemarketing survey will be commissioned by Dr. Sperry and performed by Dr. Ricci's group at the Graduate School of Public Health over a four-week period. This survey will be completed for 500 households in the zip codes where we intend to conduct this study. Demographics of the respondents will resemble the demographics of the region. Respondents will discuss the study for 10-15 minutes with the interviewer. In previous communications of this nature, one of the most informative aspects of this exercise is the detailed, verbatim responses provided from individuals both in favor and opposed to this research. This information will be provided to the IRB for review.

- **Opt out bracelets:** Prehospital providers will be trained to identify "OPT OUT "bracelets and to not include these patients in our research study.

- **Jehovah's Witness Congregations:** In the past we have noted a special interest from Jehovah's Witness Congregations in any blood product administration EFIC trials. Therefore, we plan to send a letter and instructions for an opt out bracelet to congregations in our community.

In summary, we will make a significant effort to disclose the study to the public and to receive feedback from the community about the study. We will document all comments and reach as many people as possible. These results will be reported to the IRB. We will keep the research line open throughout the study for any comments.

Appendix 4 Requirements for Exception From Consent For Emergency Research

We have outlined below each criterion stipulated in the regulations for this exception and how our study design applies to these criteria.

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

The proposed trial is a randomized trial comparing the use of prehospital through in-hospital whole blood versus standard of care in patients in hemorrhagic shock following injury requiring air medical transport to a definitive trauma center. These patients are in a life-threatening situation with a mortality before discharge approaching 30-40% despite all efforts. The standard of care for management of these patients includes intravenous crystalloid and packed red blood cells while en-route to definitive care and component resuscitation once arrival occurs at the trauma center.

Importantly, prior studies have demonstrated that injured patients who require large volume blood transfusion have improved survival if transfusion of high or equal ratios of plasma and platelets to blood occurs. Evidence suggests that early blood component transfusion may reduce overall blood transfusion requirements and that addressing the coagulopathy which occurs early after injury improves outcome. This is essentially what whole blood resuscitation provides.

(2) Obtaining informed consent is not feasible because:
i. The subjects will not be able to give their informed consent as a result of their medical condition;
ii. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

The study intervention needs to be administered en-route to a definitive trauma center from the injury scene or from a referring hospital (see discussion of therapeutic window below). In this uncontrolled setting, the hemorrhagic shock patient is unable to provide consent for study enrollment, is commonly unconscious or in extremis, and legal next-of-kin are often not immediately available at the scene, nor is it practical for the hospital provider to explain the study and receive consent while caring for the patient. Since we are studying patients with hemorrhagic shock following injury, there is no way to prospectively identify individuals who are likely to become eligible for this trial.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:
i. Subjects are facing a life-threatening situation that necessitates intervention;
ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(i) As defined, these patients are injured and in hemorraghic shock and are facing a potentially

life-threatening situation that requires immediate intervention.
(ii) Previous human studies suggest the potential for a direct benefit to individual patients who are in hemorrhagic shock.
(iii) Whole blood has been evaluated in the military and has been shown to offer a survival advantage. We have provided whole blood to over 230 patients without complication or incident. As discussed above, there are potential risks to subjects that may have not been observed in previous trials. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal and the current poor outcome for patients with hemorrhagic shock.

(4) The clinical investigation could not practicably be carried out without the waiver.

This study could not be conducted without the waiver of consent due to the need to initiate the intervention in the prehospital setting en route to a definitive trauma center for patients in hemorrhagic shock at significant risk of mortality.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

Patients in hemorrhagic shock following injury have been shown to develop progressive hypothermia, coagulopathy and acidosis leading to further recalcitrant hemorrhage and multisystem organ failure and death. The potential therapeutic window for addressing this process is during the initial resuscitation period, which occurs from arrival of the air medical transport provider on scene or at a referral hospital up until trauma center arrival. Since this is an immediately life-threatening situation, it will not always be possible to contact legal representatives at the time of study entry. We will make every effort to contact legal representatives after admission to the hospital to notify them that the patient was enrolled in a randomized trial. Research personnel will attempt to contact the subject's legal authorized representative as soon as feasible and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period then he/she will be approached by research personnel for notification of enrollment.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

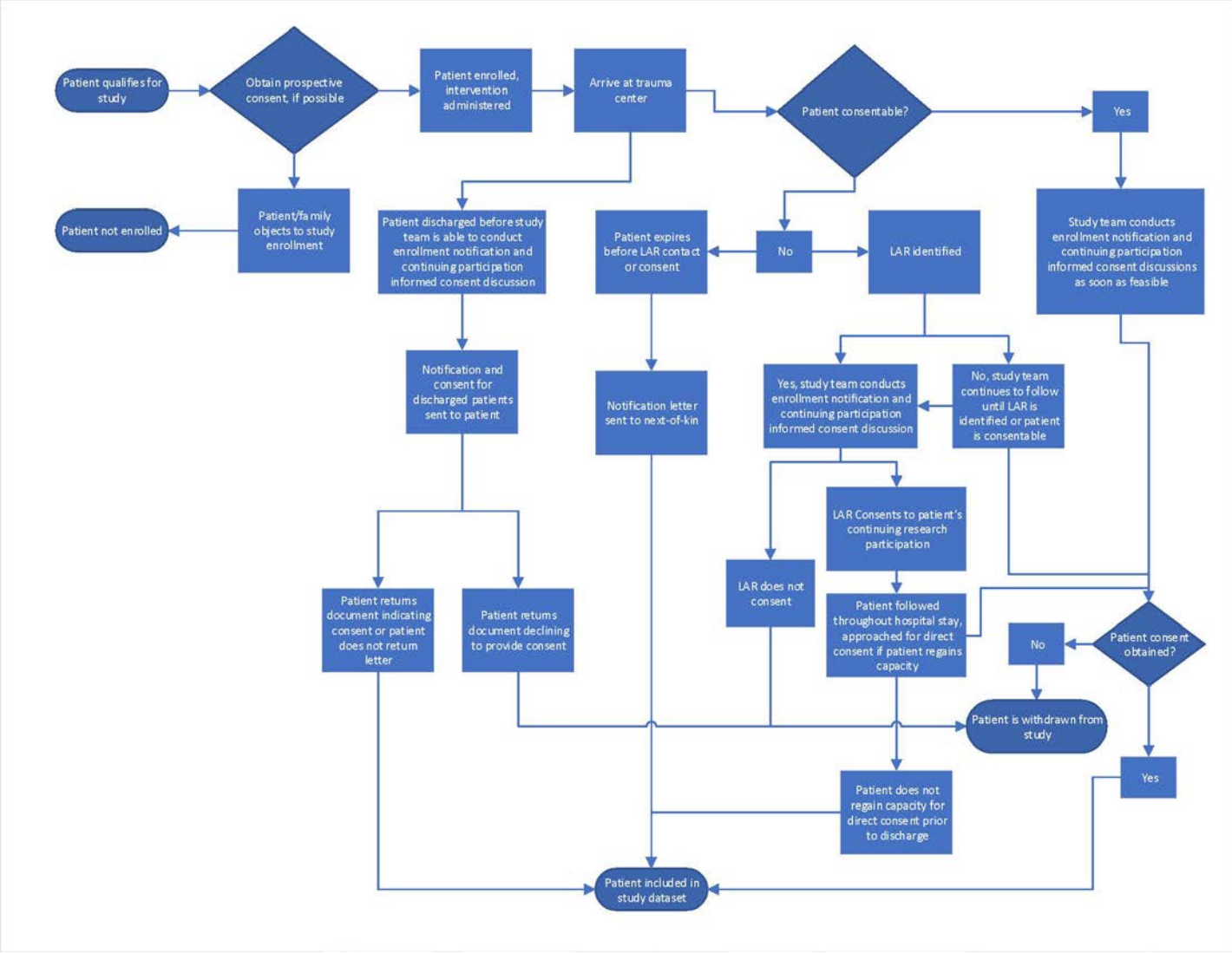
All procedures and consent forms will be approved by the Institutional Review Board (IRB) of the study site prior to the onset of the trial.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted

and from which the subjects will be drawn;
ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
iv. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
v. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(i) Community consultation as outlined by the local IRB will be undertaken prior to IRB approval. Since the population eligible for enrollment includes all citizens in the study region it will not be possible to target any particular small group. Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. If requested, bracelets will be made available that could be worn by members of the community who do not want to participate. Public notification and community consultation will be performed as directed by the local IRB and may include such methods as using random digit dialing telephone surveys of the proposed study community, targeted small group meetings or consultation with community leaders. Our institution has significant experience with community consultation and notification practices.
(ii) & (iii) Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the investigators. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study.
(iv) The Data Safety Monitoring Board will function as an independent data monitoring committee who will exercise oversight of the study.
(v) We expect that all patients who meet the enrollment criteria will be unconscious or in critical state that does not allow appropriate consent to occur. Any delay in medical care that would be required for the care provider to attempt to obtain consent from the patient’s legal guardian would be life threatening. Thus it will not be feasible to attempt to obtain informed consent during the initial therapeutic window. Requiring consent to review a hospital chart to determine the presence or absence of serious adverse events is likely to be associated with a biased estimate of the safety and efficacy of the intervention. Therefore we will use exception from consent for emergency research which includes public notification, community consultation, patient notification of enrollment, and provision of an opportunity to opt out from ongoing participation.

Appendix 5 Standard operation procedures for notification and consent in EFIC



DONOR-PATIENT "LOOKBACK"

APPROVALS

All Approvals are maintained and controlled via Document Control Systems' MC3 Portal™ Software. Please Refer to MC3 Portal™ for the current controlled revision and approval records.

SUMMARY OF THE MODIFICATIONS – See MASTERControl™ InfoCard Release Date

List a summary of the modifications below. Bullet outline is recommended.

- **Revised Principle:** Regulatory agencies require notification of consignees by donor centers of blood products from a donor who subsequently tests confirmed positive for HIV1, 2, HCV, ~~or HTLV-I/II~~ or is at risk for transmitting Creutzfeldt-Jakob disease (CJD). Lookback will also be performed by CTS when notified by the blood center of donors confirmed positive for HBV, **HTLV**, WNV, Zika, and Ebola viruses and Babesia.

- **Revised Section II title and step II.A: RECIPIENTS PHYSICIAN NOTIFICATION OF POSSIBLE VIRAL/CJD/PARASITIC INFECTION (HIV, HCV, HBV, HTLV, WNV, Zika, Ebola, CJD, Babesia ~~Ebola)~~**
  A. General Requirements: FDA has specific lookback requirements for some infectious agents, e.g., HIV, HCV, CJD, while others are performed by CTS as being important for patient safety (HVB, HTLV, WNV, Zika, Ebola, Babesia). The CTS Pittsburgh and Chicago physician will identify a transfusion recipient according to records available described in Section IV of this policy. Transfusion Service physician will send the patient's physician a letter **or secure e-mail** notifying him/her of the lookback. HIV and HCV notifications are sent by certified mail **or secure e-mail. The rest of the notification letters are sent by regular mail or secure e-mail.**

- **Revised step II.B.1; step II.B.5 rewritten**
  B. Lookback Notification Process
     1. **HIV and HCV lookback process**: A notification letter is sent along with a notification form **by certified mail or secure e-mail**. The physician must promptly return the enclosed notification form …
     5. **CJD lookback notification process and criteria:** The blood center will notify CTS of components from donors that were found to have CJD, vCJD, suspected vCJD, risk factors for CJD, or if withdrawal is recommended in cases under investigation for vCJD (CJD diagnosis and age less than 55). In those situations, consignee notification could enable the consignee to inform the physician, or other qualified personnel responsible for care of the recipients, so that recipient tracing and medically appropriate notification and counseling may be performed at the discretion of health care providers. CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required. For transfusible components from a donor with one family member diagnosed with CJD, or with risk factors for vCJD, suspected vCJD (due to geographic risk deferral, transfusion in the U.K. or in France between 1980 and the present, or due to injection of bovine insulin), per FDA Guidance for Industry, it is not appropriate to conduct tracing and notification of recipients of prior donations.

(Continued on next page)

- **Revised step V.A.4**

V. **RECORDS**

A. The following documents are maintained in the lookback file.

4. Certified mail receipts **or print out of secure e-mail communication.**

D. Lookback records are maintained **for 10 years**.

E. HCV and HIV lookbacks are discussed at Transfusion Committee meetings and they are documented in Transfusion Committee records.

- **Deleted Procedure Notes 2-4**

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ITxM The Institute for Transfusion Medicine clinical services	**Donor-Patient "Lookback"**		Pg. 46 of 8
	Doc #: ITxM-CS-00795	Revision: 16	
	Department: ITxM Clinical Services		

PROCESS

SYSTEM

Investigation of Adverse Transfusion Effects, Information Management

CRITICAL CONTROL POINT

Documentation/Record Keeping, Supplier Qualification, Error/Accident Review, Internal Assessment, Process Improvement

PRINCIPLE

Regulatory agencies require notification of consignees by donor centers of blood products from a donor who subsequently tests confirmed positive for HIV1, 2, HCV, or is at risk for transmitting Creutzfeldt-Jakob disease (CJD). Lookback will also be performed by CTS when notified by the blood center of donors confirmed positive for HBV, HTLV, WNV, Zika, and Ebola viruses and Babesia.

POLICY

I. IDENTIFICATION OF INFECTED DONORS

A. Units implicated in the lookback process are identified by the blood center according to their SOPs. The transfusion service is notified in writing of the units and their shipping date. Notification to external hospitals (non CTS facilities) is completed by the blood center, not the RCRL or CTS.

II. RECIPIENTS PHYSICIAN NOTIFICATION OF POSSIBLE VIRAL/CJD/PARASITIC INFECTION (HIV, HCV, HBV, HTLV, WNV, Zika, Ebola, CJD,Babesia)

A. General Requirements

FDA has specific lookback requirements for some infectious agents, e.g., HIV, HCV, CJD, while others are performed by CTS as being important for patient safety (HVB, HTLV, WNV, Zika, Ebola, Babesia). The CTS Pittsburgh and Chicago physician will identify a transfusion recipient according to records available described in Section IV of this policy. Transfusion Service physician will send the patient's physician a letter or secure e-mail notifying him/her of the lookback. HIV and HCV notifications are sent by certified mail or secure e-mail. The rest of the notification letters are sent by regular mail or secure e-mail.

B. Lookback Notification Process

1. **HIV and HCV lookback process**: A notification letter is sent along with a notification form by certified mail or secure e-mail. The physician must promptly return the enclosed notification form to the transfusion service indicating that they accept responsibility for patient notification. In the case of HIV and HCV, patient notification includes the need for HIV or HCV testing and counseling. If the transfusion service cannot locate the physician, does not receive the notification form from the physician, or the physician refuses to accept responsibility for notification, then the transfusion service is responsible for notifying the patient. This is done by the CTS physician at CTS hospitals. The FDA requires that the process of notification be completed within 12 weeks for HCV and HIV and reasonable attempts should be made. In addition to the physician notification, the facility where the patient was transfused will be notified. This notification will go to the transfusion committee or similar entity at the facility.

2. **HCV lookback notification criteria:** A reactive NAT result serves as one basis for initiating lookback. Since confirmatory testing for HCV (RIBA) became unavailable in 2012, new FDA approved algorithms were developed for HCV notification. Notification of transfusion recipients of prior collections from the same donor is not required when the donor is repeatedly reactive on the anti-HCV screening assay but negative on a mini-pool or individual donation HCV NAT assay and non-reactive on a second anti-HCV screening assay. Transfusion Services must make reasonable attempts to perform the notification within 12 weeks when the donor is repeatedly reactive on the anti-HCV screening assay and positive on a mini-pool or individual donation HCV NAT assay or negative on the HCV NAT assay and reactive on the second anti-HCV screening assay. Notification for HCV is not required if the donor is deceased.

3. **HIV lookback notification criteria**: When testing for HIV is confirmed positive or NAT positive when the screening test is reactive and further testing is not available, or if under an IND or IDE is exempted for such use by FDA, you

must notify transfusion recipients of previous collections of blood and blood components at increased risk of transmitting HIV infection, or the recipient's physician of record or a legal representative or relative if the recipient is a minor, deceased, adjudged incompetent by a State court, or if the recipient is competent but State law permits a legal representative or relative to receive information on behalf of the recipient of the need for recipient HIV testing and counseling (see above), you must make reasonable attempts to perform the notification within 12 weeks after receiving the results of further testing for evidence of HIV infection from the collecting establishment . If the recipient received a transfusion in the hospital and died without ever being discharged from the hospital, you must notify the recipient's physician of record but it is left up to the clinician's medical judgement as to whether or not to inform a family member.

4. **HBV lookback notification process and criteria:** The blood center will notify CTS of components from donors that test confirmed positive for HBV on a current donation (surface antigen positive with positive neutralization and/or positive NAT). CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome and/or testing. Follow up physician notification is not required if no response is received. If the patient is deceased, physician notification is not required.
5. **CJD lookback notification process and criteria:** The blood center will notify CTS of components from donors that were found to have CJD, vCJD, suspected vCJD, risk factors for CJD, or if withdrawal is recommended in cases under investigation for vCJD (CJD diagnosis and age less than 55). In those situations, consignee notification could enable the consignee to inform the physician, or other qualified personnel responsible for care of the recipients, so that recipient tracing and medically appropriate notification and counseling may be performed at the discretion of health care providers. CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required.

   For transfusible components from a donor with one family member diagnosed with CJD, or with risk factors for vCJD, suspected vCJD (due to geographic risk deferral, transfusion in the U.K. or in France between 1980 and the present, or due to injection of bovine insulin), per FDA Guidance for Industry, it is not appropriate to conduct tracing and notification of recipients of prior donations.

6. **HTLV I/II lookback notification process and criteria:** The blood center will notify CTS of components from donors that test confirmed positive for HTLV I/II. CTS will notify the patient's physician in writing by letter or secure

email and request that he/she provides follow up to the transfusion service of the patient outcome and/or testing. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required.

7. **Zika virus lookback notification process and criteria:** The blood center will notify CTS of components from donors that test NAT positive for Zika virus. CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome and/or testing. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required.
8. **WNV virus lookback notification process and criteria:** The blood center will notify CTS of components from donors that test NAT positive for WNV virus. CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome and/or testing. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required.
9. **Ebola virus lookback notification process and criteria:** The blood center will notify CTS regarding blood and blood components collected from donors later determined to have Ebola virus infection or disease. CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome and/or testing. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required.
10. **Babesia lookback notification process and criteria:** The blood center will notify CTS of components from donors that test positive by EIA only or EIA and NAT. CTS will notify the patient's physician in writing by letter or secure email and request that he/she provides follow up to the transfusion service of the patient outcome and/or testing. Follow up notification is not required if no response is received. If the patient is deceased, physician notification is not required.

III. CENTRALIZED TRANSFUSION SERVICE RECIPIENT IDENTIFICATION

The transfusion service must identify the recipient of any of the implicated units. The method of recipient tracing varies with the date of transfusion and the hospital.

PUH/E&E/CHP - After May 21, 1999 - SafeTrace Tx contains all units receipts received.
Between mid-October 1988 and May 20, 1999 - the PTS computer system or microfiche contains all units recipients received.
Prior to PTS computer (1988) - unit inventory cards (3 x 5) were used to record each unit, to whom it was issued and the hospital. Cards are stored in boxes stored in a warehouse at National Business Records Management (NBRM). There are cards dating back at least to 1977. (see Notes for retrieving cards)

MUH - Patients transfused after May 11, 1991 are in the PTS system. MUH has no transfusion records prior to this date.

ALLEGHENY GENERAL HOSPITAL - Patients transfused after May 21, 1999 are in SafeTrace Tx. Patients transfused between August 20, 1994 and May 20, 1999 are in the PTS system. Patients transfused prior to this date must be retrieved by AGH staff. From September 17, 1988 to August 19, 1994 records are at AGH Information Systems (SunQuest System). From March 14, 1979 to September 16, 1988 , records are in log books stored at AGH Stat lab. Any additional records are stored at Iron Mountain. A request for the required records should be sent to the medical director of the department of pathology and the LIS manager.

SHADYSIDE HOSPITAL - Patients transfused after May 21, 1999 are in SafeTrace Tx. Patients transfused between October 7, 1994 and May 20, 1999 are in the PTS system. Patients transfused on or prior to this date must be extracted by SSH staff. A request for the required records should be sent to the medical director of the department of pathology and the laboratory administrative director.

WASHINGTON HOSPITAL - Patients transfused after May 21, 1999 are in SafeTrace Tx. Patients transfused between July 7, 1995 and May 20, 1999 are in the PTS system. Patients transfused prior to this date are in card files and will be retrieved by WH staff. A request for the required records should be sent to the medical director of the department of pathology and the lab manager.

MCKEESPORT HOSPITAL - Patients transfused after May 21, 1999 are in SafeTrace Tx. Patients transfused between March 2, 1997 and May 20, 1999 are in the PTS system. Patients transfused on or prior to this date are in card files and will be retrieved by McK staff. A request for the required records should be sent to the medical director of the department of pathology and the lab manager.

UPMC, SOUTH SIDE HOSPITAL - Patients transfused after May 21, 1999 are in SafeTrace Tx. Patients transfused between February 28, 1997 and May 20, 1999 are in the PTS system. Patients transfused on or prior to this date are in card files and will be retrieved by SOSH staff. A request for the required records should be sent to the medical director of the department of pathology and the lab manager.

COMMUNITY MEDICAL CENTER - Patients transfused on or after October 5, 1999 are in the SafeTrace Tx system. Patients transfused prior to this date are referred to the medical director/lab manager to obtain the required information.

UPMC, ST. MARGARETS - Patients transfused after July 31, 2000 are in the SafeTrace Tx system. Patients transfused on or prior to this date are referred to the medical director/lab manager to obtain the required information.

MAGEE HOSPITAL - Patients transfused after December 10, 2000 are in SafeTrace Tx. Patients transfused on or prior to this date are referred to the medical director/lab manager of the hospital.

WEST PENN HOSPITAL - Patients transfused after November 19, 2000 are in SafeTrace Tx. Patients transfused on or prior to this date are referred to the medical director/lab manager of the hospital.

LIFECARE HOSPITAL - Patients transfused after January 17, 2000 are in SafeTrace Tx. Patients transfused on or prior to this date are referred to the medical director/lab manager of the hospital.

KINDRED HOSPITAL - Patients transfused after December 31, 1999 are in SafeTrace Tx. Patients transfused on or prior to this date are referred to the medical director/lab manager of the hospital.

RCRL CHICAGO - Patient's transfused after June 1, 2000 are in SafeTrace Tx. For patient's transfused prior to this date, LifeSource will contact the transfusing facility directly.

UPMC-BRADDOCK HOSPITAL – Patients transfused after September 16, 2001 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

FORBES REGIONAL HOSPITAL – Patients transfused after March 24, 2002 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

UPMC PASSAVANT AND UPMC PASSAVANT CRANBERRY HOSPITAL – Patients transfused after October 31, 2004 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

AGH-SUBURBAN CAMPUS – Patients transfused after March 15, 2006, are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

UPMC MERCY – Patients transfused after December 1, 2008 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

LIFELINE – Patients transfused after December 1, 2009 are in SafeTrace Tx.

ADVANCED SURGICAL – Patients transfused after May 1, 2010 are in SafeTrace Tx.

MEADVILLE MEDICAL CENTER – Patients transfused after March 15, 2012 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

UPMC EAST – Patients transfused after July 2, 2012 are in SafeTrace Tx. UPMC East has no transfusion records prior to this date.

WHEELING HOSPITAL – Patients transfused after January 11, 2014 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

BELMONT COMMUNITY HOSPITAL – Patients transfused after January 29, 2014 are in SafeTrace Tx. Patients transfused prior to this date are referred to the lab manager of the hospital.

ALLEGHENY VALLEY HOSPITAL – Patients transfused on or after March 15, 2014 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

CANONSBURG GENERAL HOSPITAL - Patients transfused on or after March 15, 2014 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

REYNOLDS MEMORIAL HOSPITAL – Patients transfused on or after July 28, 2014 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

JEFFERSON HOSPITAL – Patients transfused on or after April 25, 2015 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

WASHINGTON HEALTH SYSTEM-GREENE – Patients transfused on or after December 1, 2016 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

UPMC HORIZON-GREENVILLE – Patients transfused on or after January 17, 2017 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

UPMC HORIZON-SHENANGO – Patients transfused on or after January 17, 2017 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

UNIVERSITY OF ILLINOIS-CHICAGO – Patients transfused on or after February 15, 2014 are in SafeTrace Tx. Patients transfused prior to this date are referred to the medical director/lab manager of the hospital.

IV. CONFIRMING THE PATIENT AND IDENTIFYING THE PHYSICIAN

A. Pittsburgh: For patients since October 1988, the SafeTrace Tx has the patient's name, hospital number, birth date and sometimes the physician. If the physician's name is not available in the computer, this must be obtained from the medical record. For transfusions in the pre-computer era, the transfusion, the recipient, and the physician are verified by review of the medical record or by the PTS patient card. Patient cards are stored in boxes stored in a warehouse at National Business Records Management (NBRM).

B. Chicago: Patients transfused after June 1, 2000 are in SafeTrace Tx. If physician information is not in SafeTrace Tx, the transfusion entity will receive only the information available prior to this time.

V. RECORDS

A. The following documents are maintained in the lookback file:

1. Notification letter from blood center
2. Copy of certified letter notifying recipient's physician (HIV, HCV)
3. Documentation indicating physician's acceptance of responsibility for patient notification (HIV, HCV only)
4. Certified mail receipts or a print out of secure e-mail communication
5. Documentation of patient notification if performed by the transfusion service medical director

B. Documentation of notification of the patient's physician

C. Documentation of notification of the patient by his/her physician should be maintained in the patient's medical record

D. Lookback records are maintained for 10 years.

E. HCV and HIV lookbacks are discussed at Transfusion Committee meetings and they are documented in Transfusion Committee records.

PROCEDURE NOTES

1. Electronic records in SafeTrace Tx date back to May 20 of 1999. Prior to this date, information may be retrieved using the Cognos PTS Archive reports if data is available.

REFERENCES

1. 21CFR 610.47(b)(3)
2. 21CFR 610.46

3. Guidance for Industry "Lookback" for Hepatitis C Virus (HCV): Product Quarantine, Consignee, Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV, December 2010. Updated August 2017.
4. 21CFR 610.46
5. Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components, Including Source Plasma, to Reduce the Risk of Transmission of Hepatitis B Virus, October 2012.
6. Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products. Guidance for Industry, May 2010. Updated January 2016.
7. "Lookback" for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV, August 2007. Updated December 2010.
8. Guidance for Industry: Donor Screening for Antibodies to HTLV-II. August 1997.

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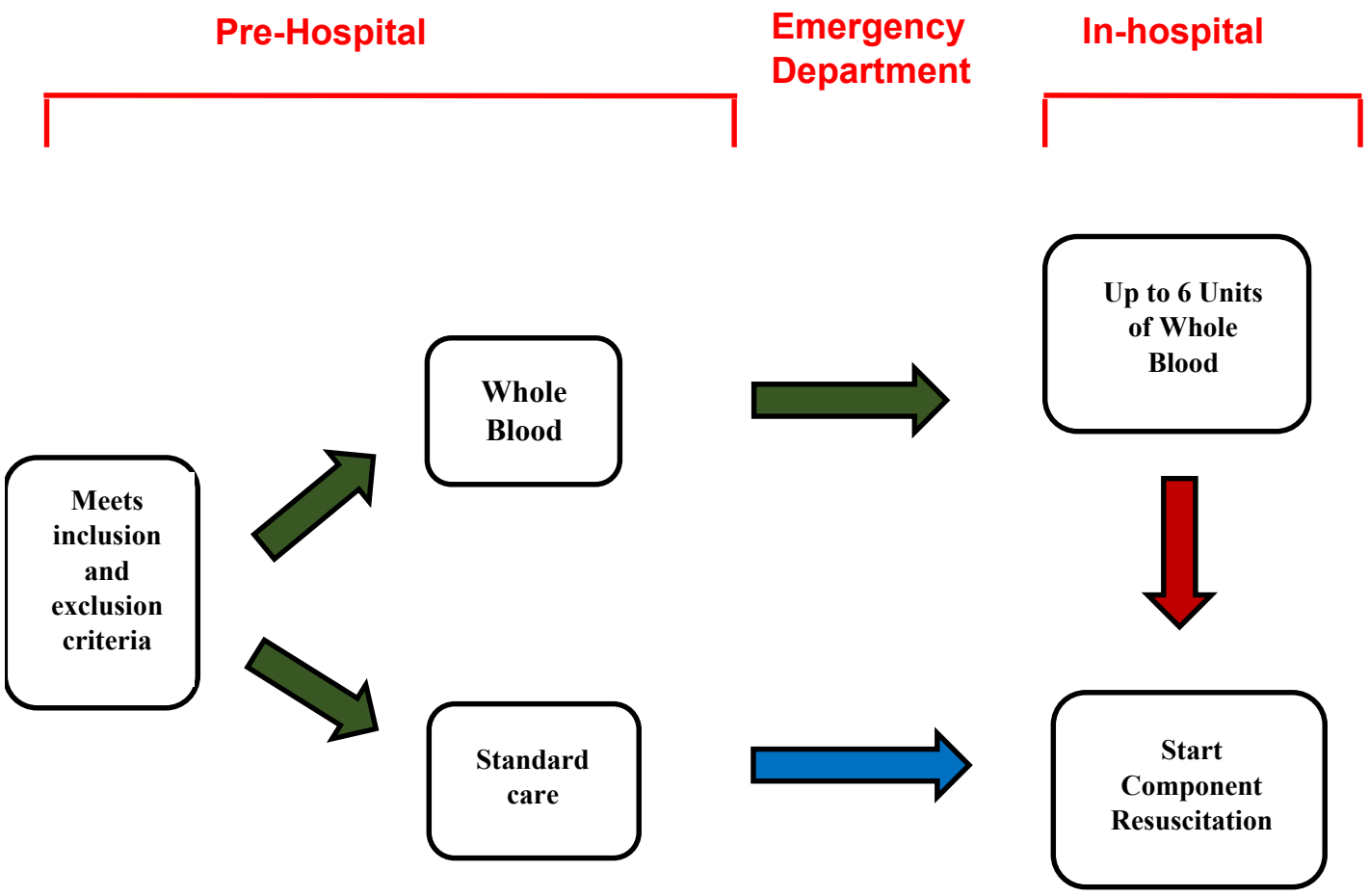
Appendix 7:

PPOWER Flow Chart



APPENDIX 8: Tables that will be used to summarize study data and comparisons:

Table1: Demographics and injury

	Overall	Arm A Standard of Care n=	Arm B LTLR-WB n=	
Age Mean ± SD Median (IQR)				
Sex Males, frequency(%) Females frequency(%)				
Race White: Black: Others:				
BMI				
Major comorbidity 1. 2 3. 4.				
Smoking				
Intoxicated (alcohol)				
GCS				
Mechanism of injury				
Blunt vs Penetration				
ISS				
AIS				
Head trauma				
Distance from scene to hospital				
Transferred				
sedated				
Intubated				
ED Disposition				
Procedures				

Table 2: Safety and Efficacy

		Overall	Arm A Standard of Care	Arm B LTLR-WB	Testing
In hospital Mortality Frequency (%)					

In hospital Mortality Proportion in each arm					Z test of independent proportion
Median survival at 3hr 6hr 24hr 28days					Log rank test

Table 3: Eligibility, Enrollment, and Subject Accrual

	Overall	Arm A Standard of Care	Arm B LTLR-WB	95% C.I
Patients that meet the eligibility criteria for the trial Frequency, (%) and Proportion				
Eligible patients that can be randomized Frequency, (%) and Proportion				
Eligible patients who are enrolled in the trial Frequency, (%) and Proportion				
Patients eligible but not enrolled Frequency, (%) and Proportion				
Patients randomized but not included in the study Frequency, (%) and Proportion				
Rate of subjects' accrual per month Frequency, (%) and Proportion/ month				
Adherence rates for each treatment arm Frequency, (%) and Proportion				
Reasons of not enrollment 1. 2. 3. 4. 5. Frequency, (%) and Proportion				

Table 4: Estimates for Trial Secondary Clinical Outcomes

	Overall	Arm A Standard of Care	Arm B LTLR-WB	95% C.I
Average Denver post-injury MOF score derived from the 3 highest daily scores.				
MOF free days across the study two arms				

ARDS (Frequency, (%) and Proportion)				
NI (Frequency, (%) and Proportion)				
Mortality 6hr 24hr 28day (Frequency, (%) and Proportion)				
Hemolytic transfusion reactions (Frequency, (%) and Proportion)				
Median Survival analysis for in relation to all causes of death				
Blood component transfused the initial 24 hours (units) PRBC: Plasma: Platelets: Cryoprecipitate:				
Total resuscitation volumes over the initial 24 hours (Units)				
Length of ICU stay (Days)				
Days on a ventilator (Days)				
Total hospital stay (Days)				

Table 5: Unanticipated Events

Unanticipated Events Reporting: grade/severity, PI Assessment: Related/unrelated	Overall F(%)	Arm A Standard of Care F(%)	Arm B LTLR-WB F(%)	
1.				
2.				
3.				
4.				
5.				

Table 6: Protocol deviation

Protocol deviation	Overall F(%)	Arm A Standard of Care F(%)	Arm B LTLR-WB F(%)	
1.				
2.				
3.				
4.				
5.				