PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Manual of Operations

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Chapter 1 Overview

Section 1.1 Contact Information

Houston Clinical Coordinating Center (HCCC)
Principal Investigator:
John B. Holcomb, MD, FACS
Vice Chair and Professor of Surgery/Chief, Division of Acute Care Surgery
Director, Center for Translational Injury Research
Jack H. Mayfield, M.D. Chair in Surgery
University of Texas Health Science Center at Houston
6410 Fannin, Suite 1100 Houston, TX, 77030
Phone: 713-500-5493
Fax: 713-512-7135
John.Holcomb@uth.tmc.edu

Co-Investigators:
Charles Wade, PhD
Professor of Surgery
University of Texas Health Science Center at Houston
Phone: 713-500-5391
Charles.E.Wade@uth.tmc.edu

Deborah del Junco, PhD
Associate Professor of Surgery
University of Texas Health Science Center at Houston
Phone: 713-500-7902
Deborah.J.DelJunco@uth.tmc.edu

Nena Matijevic, PhD
Associate Professor of Surgery
University of Texas Health Science Center at Houston
Phone: 713-500-6807
Nena.Matijevic@uth.tmc.edu

Erin Fox, PhD
Assistant Professor of Surgery
University of Texas Health Science Center at Houston
Phone: 713-500-7965
Erin.E.Fox@uth.tmc.edu

Project Manager:
Jeanette Podbielski, RN
Research Program Manager
University of Texas Health Science Center at Houston
Phone: 713-500-6407
Fax: 713-512-7135
Jeanette.M.Podbielski@uth.tmc.edu

Angela Beeler
Assistant Project Manager
University of Texas Health Science Center at Houston
Phone: 713-500-5395
Angela.Beeler@uth.tmc.edu

Administrative:
Xiang Fang, MBA, MS
Administrative Director
Center for Translational Injury Research (CeTIR), UTHealth
6410 Fannin, UPB 1100.26
Houston, TX 77030
Tel: 713-500-5428
Email: Xiang.Fang@uth.tmc.edu

Bea Flato
Senior Executive Assistant
CeTIR, UTHealth
6410 Fannin, UPB 1100
Houston, TX 77030
713-500-7313
Email: Beatrice.Flato@uth.tmc.edu

Serena Cooper
Senior Administrative Coordinator
CeTIR, UTHealth
6410 Fannin, UPB 1100
Houston, TX 77030
713-500-5493
Email: Serena.Cooper@uth.tmc.edu

Houston Data Coordinating Center (HDCC)
Principal Investigator:
Barbara C. Tilley, PhD
Lorne C. Bain Distinguished Professor and Director
Division of Biostatistics
University of Texas Health Science Center at Houston, School of Public Health
1200 Herman Pressler Dr., RAS E833
Houston, TX 77030
Phone: 713 500-9564
Fax: 713 500-9530
Barabara.C.Tilley@uth.tmc.edu

Co-Investigators:
Sarah Baraniuk, PhD
Assistant Professor for Biostatistics
University of Texas Health Science Center at Houston, School of Public Health
1200 Herman Pressler Dr., RAS E807
Houston, TX 77030
Phone: 713 500-9512
Email: Mary.S.Baraniuk@uth.tmc.edu

Data Research Associate:
Joshua Nixon, MS
Division of Biostatistics
UTHSC-Houston School of Public Health
1200 Herman Pressler Drive, RAS W824
Houston, Texas 77030
Phone: 713-500-9576
Email: Joshua.L.Nixon@uth.tmc.edu

Regulatory Coordinator:
Claudette Okorafor, MHA
Division of Biostatistics
UTHSC-Houston School of Public Health
1200 Herman Pressler Drive, RAS W824
Houston, Texas 77030
Phone: 713-500-9579
Email: Claudette.P.Okorafor@uth.tmc.edu

Resuscitation Outcome Consortium (ROC)
Principal Investigator:
Gerald van Belle, PhD
Resuscitation Outcome Consortium (ROC) Professor
Department of Biostatistics and Environmental and Occupational Health Sciences
University of Washington
Seattle, Washington 98195-7232
Phone: 206-221-4185
Email: vanbelle@uw.edu

Project Manager:
Kellie Sheehan, RN, BSN
ROC Clinical Trial Center
University of Washington
1107 NE 45th St. Suite 505
Seattle, WA 98105
Phone: 206-616-0437
email: kelliesj@u.washington.edu

Project Director:
Judy Powell, BSN
University of Washington
ROC Clinical Trial Center
Seattle, WA 98105
Phone: 206 685-1302
Email: jlpowell@uw.edu

Biostatistician:
Brian LeRoux, PhD
University of Washington
ROC Clinical Trial Center
1107 N.E. 45th St., Suite 505
Seattle, WA 98105
Phone: 206 685-1302
Email: leroux@uw.edu

PROPPR
Clinical Site Contact Information

24-HOUR CLINICAL HOTLINE:
832-649-1574

Memorial Hermann Hospital/University of Texas Health Science Center at Houston
PI: Bryan Cotton, MD, MPH
Phone: 713-500-7354
Email: Bryan.A.Cotton@uth.tmc.edu

Coordinators:
Laura Vincent
Phone: 713-500-5216
Email: Laura.E.Vincent@uth.tmc.edu

Tiffany Poole
Phone: 713-500-7298
Email: Tiffany.M.McCracken@uth.tmc.edu

University of California, San Francisco
PI: Mitch Cohen, MD
Phone: 415-206-3764
Email: mcohen@sfghsurg.ucsf.edu

Coordinators:
Mary Nelson, RN, MPA
Phone: 415-206-4012
Email: nelsonm@sfghsurg.ucsf.edu

Britt Redick
Phone: 415-206-4644
Email: redickb@sfghsurg.ucsf.edu

Amanda Conroy
Phone: 415-206-4638
Email: conroya@sfghsurg.ucsf.edu

University Hospital Cincinnati
PI: Peter Muskat, MD
Phone: 513-558-5661
Email: muskatp@UCMAIL.UC.EDU

Coordinators:
Dina Gomaa
Phone: 513-558-6305
Emial: Dina.gomaa@uc.edu

Chris Barczak
Phone: 513-558-8091
Email: barczacm@ucmail.uc.edu

Sunnybrook Health Sciences Centre/University of Toronto
PI: Sandro Rizoli, MD
Phone: 416-480-5255
Email: Sandro.Rizoli@sunnybrook.ca

Coordinators:
Sandy Trpcic
Phone: 416-480-6100 extension 7322
Email: Sandy.Trpcic@sunnybrook.ca

Skeeta Sobrian-Couroux
Phone: 416-480-6100 extension 88146
Email: skeeta.couroux@sunnybrook.ca

University of Alabama – Birmingham
PI: Jeffrey Kerby, MD
Phone: 205-996-4028
Email: Jeffrey.Kerby@ccc.uab.edu

Coordinators:
Carolyn Williams
Phone: 205-996-4982
Email: cswilliams@uabmc.edu

Shannon Stephens
Phone: 205-934-5890
Email: swstephens@uabmc.edu

Medical College of Wisconsin
PI: Karen Brasel, MD, MPH
Phone: 414-805-8624
Email: kbrasel@mcw.edu

Coordinator:
Pam Walsh
Phone: 414-805-6876
Email: pwalsh@mcw.edu

Allia Nelson
Email: allianelson@mcw.edu

Oregon Health and Science Unversity
PI: Martin Schreiber, MD
Phone: 503-494-6518
Email: schreiberm@ohsu.edu

Coordinators:
Samantha Underwood
Phone: 503-494-8481
Email: underwos@ohsu.edu

Tahnee Groat
Phone: 503-494-4315
Email: groat@ohsu.edu

University of Tennessee Health Science Center
PI: Timothy Fabian, MD
Phone: 901-448-5914
Email: tfabian@uthsc.edu

Coordinator:
Suzanne Wilson
Phone: 901-448-1133
Email: swilso34@uthsc.edu

University of Maryland Medical Center
PI: Thomas Scalea, M.D.
Phone: 410-328-8976
Email: TSCALEA@umm.edu

Coordinator:
Anthony Herrera
Phone: 410-328-0288
Email: aherrera@stapa.umm.edu

University of Arizona
PI: Terrence O'Keefe, M.D.
Phone: 520-626-0064
Email: tokeeffe@surgery.arizona.edu
Coordinator:
Laurel Rokowski
Phone: 520-626-6302
Email: laurel@email.arizona.edu

LA County/ University of Southern California Medical Center
PI: Kenji Inaba, M.D., FRCSC, FASC
Phone: 323-409-8597
Email: Kenji.Inaba@med.usc.edu

Coordinators:
Jay Zhu
Phone: 323-226-7180
Email: jzhu@usc.edu

Monica Wong
Phone: 323-409-8588
Email: monicadwong@gmail.com

Harborview Medical Center
PI: Eileen Bulger, M.D
Phone: 206-744-3696
Email: Ebulger@u.washington.edu

Coordinators:
Pat Klotz
Phone: 206-744-7724
Email: pklotz@u.wasington.edu

Lindsay Cattin
Phone: 206 744-7716
Email: cattinl@uw.edu

Section 1.2 Protocol Synopsis

Protocol Title	Pragmatic, Randomized Optimal Platelet and Plasma Ratios
Acronym	PROPPR
Trial Phase	Phase III Trial
Study Sites	At least 12 Level I Trauma Centers in the Phase III Trial
Study Period	Expected start date: March, 2012
Study Population	Trauma subjects predicted to receive massive transfusions (MTs) and enrolled within 2 hours of Emergency Department (ED) admission to Level I Trauma Centers
Objectives	***The objective of this study is to conduct a Phase III multi-site, randomized trial in subjects predicted to have a massive transfusion, comparing the effectiveness and safety of 1:1:1 transfusion ratios of plasma and platelets to red blood cells (the closest approximation to reconstituted whole blood) with the 1:1:2 ratio. The co-primary outcomes will be 24-hour and 30-day mortality. In addition, the functional laboratory and biomarker studies will comprehensively characterize trauma induced coagulation (TIC) and inflammatory milieu providing insight into biological phenotypes, dynamic changes over time and their relationship to treatment and outcome.*** The PROPPR Trial will be conducted under exception from informed consent (EFIC) and begin with a Vanguard Stage that will continue for up to six months to assess sites' ability to implement the protocol and recruit subjects. **<u>Clinical Hypotheses and Aims</u>** **Primary Clinical Aim:** To separately compare as co-primary outcomes, 24-hour mortality and 30-day mortality between 1:1:1 and 1:1:2 groups adjusting for clinical site. **Primary Clinical Hypothesis 1**: A greater proportion of subjects who are predicted to have a massive transfusion and randomized to the 1:1:1 ratio group will survive to 24 hours after Emergency Department (ED) admission compared with subjects randomized to the 1:1:2 ratio. **Primary Clinical Hypothesis 2**: A greater proportion of subjects who are predicted to have a massive transfusion and randomized to the 1:1:1 ratio group will survive to 30 days after ED admission compared with subjects randomized to the 1:1:2 ratio. **Ancillary Clinical Aim:** To compare subjects predicted to have a massive transfusion and randomized to the 1:1:1 or 1:1:2 ratio groups on a variety of ancillary clinical outcomes measured from randomization to initial hospital discharge after adjusting for site. **Ancillary Clinical Hypotheses 1:** Subjects predicted to have a massive transfusion and randomized to 1:1:1 will differ in number of hospital-free, ventilator-free, and ICU-free days from the 1:1:2 ratio group. **Ancillary Clinical Hypothesis 2:** Subjects predicted to have a massive transfusion and randomized to the 1:1:1 and 1:1:2 ratio groups will differ in time to hemostasis, major surgical procedures, and in the incidence of transfusion-related serious adverse events during initial hospitalization; will differ in the amount of study blood products given until hemostasis and in the amount of blood products given from hemostasis to 24 hours; and will differ in functional status at initial hospital discharge and in initial hospital discharge status.

	Laboratory Hypotheses and Aims **Overall Laboratory Hypothesis:** Subjects predicted to have a massive transfusion will differ in their coagulation and inflammatory phenotypes at admission and over time which will be affected by resuscitation and affect outcome. **Laboratory Aim 1:** To develop models characterizing TIC and inflammation in enrolled patients at ED admission. **Hypothesis 1:** Severely injured trauma patients enrolled into PROPPR will differ in their coagulation and inflammatory phenotypes at admission by subjects' demographic and baseline injury characteristics. **Laboratory Aim 2:** To develop models characterizing the dynamics of TIC in order to identify mechanistic drivers and sequelae of coagulation and inflammation, AND to characterize the natural history of the coagulation/inflammatory milieu in enrolled subjects. **Hypothesis 2:** Coagulation and inflammatory phenotypes identified at admission will display dynamic changes. These phenotype changes will be driven by injury demographics and resuscitation. **Laboratory Aim 3:** To assess the effect of coagulation and inflammatory models on primary and ancillary outcomes. **Hypothesis 3:** Coagulation and inflammatory profiles identified in **Laboratory Aims 1 and 2** will be associated with primary and ancillary clinical outcomes.
Background	Multiple observational studies have reported that blood product component ratios (*i.e.*, plasma:platelets:RBCs) that approach the 1:1:1 ratio, as found in fresh whole blood, are associated with significant decreases in truncal hemorrhagic death and in overall 24-hour and 30-day mortality among injured patients. The rationale for the 1:1:1 ratio is that the closer a transfusion regimen approximates whole blood, the faster hemostasis will be achieved with minimum risk of coagulopathy. The current DoD guideline specifies the use of 1:1:1, and this practice is followed in almost all combat casualties. In other observational studies, leading centers have reported good outcomes across a range of different blood product ratios. For example, a 1:2 plasma:RBC ratio is used with little guidance regarding platelets. The American Association of Blood Banks (AABB) recently performed a meta-analysis and recommended the use of at least a 1:3 plasma:RBC ratio in Level I trauma centers until randomized trials can provide more definitive evidence. The proposed randomized trial is intended to resolve debate and uncertainty regarding optimum blood product ratios. Trauma induced coagulopathy (TIC) is the global term that describes coagulopathy after injury and the associated sequalae. Despite identification and quantification of this coagulopathy, the initiators of the process, underlying mechanisms, interaction of different coagulopathy phenotypes and their specific relationships to treatment and outcomes remain poorly understood and are a priority research area for the management of trauma hemorrhage. Brohi and Cohen have recently described a proposed mechanism for this TIC based on the protein C pathway. However, a definitive causal link has not been established. Several recent publications have documented the lack of understanding in this critical arena. Underlying the continuing controversy in trauma resuscitation research are two main concerns: transfusion-related complications and survival/selection bias. Some studies have shown decreased rates of complications from multiple organ failure (MOF) with increased ratios of blood products, while others have documented increased MOF rates. A few studies recorded data only on patients who survived at least 48 hours, focusing on inflammatory outcomes of acute respiratory distress syndrome (ARDS) and MOF. Other studies excluded only those patients who died in the first 30 minutes after Emergency Department (ED)

	arrival. Because most preventable hemorrhagic deaths occur within hours of trauma patients' ED arrival, it is critical to evaluate both the short- as well as longer-term effects of blood product transfusions. Therefore the longer a bleeding patient survives, the greater the chance to receive a cumulative ratio approaching 1:1:1 (survival bias). **The proposed multi-center, randomized trial with a Vanguard Stage and intent-to-treat (ITT) analyses based on appropriate short- and long-term outcomes will 1) address the survival and selection bias that plagues previous studies, and 2) provide a more complete picture of the effectivenessand safety of 1:1:1 vs. 1:1:2 blood product ratios over the time windows of trauma patients' greatest potential benefit and risk.**
Study Design	Randomized, two-group, controlled Phase III trial with a Vanguard stage. Equal random allocation to treatment using stratified, permuted blocks with randomly chosen block sizes and stratification by site.
Subject Inclusion Criteria	*To be eligible, subjects must meet all of the following:* 1) Required the highest trauma team activation; 2) estimated age 15 years or older or greater than/equal to weight of 50 kg if age unknown; 3) received directly from the injury scene; 4) initiated transfusion of at least one unit of blood component within the first hour of arrival or during prehospital transport; 5) predicted to receive a MT by exceeding the threshold score of *either* the ABC score or the attending trauma physician's judgment criteria.
Subject Exclusion Criteria	*Subjects are ineligible if they meet one or more of the following:* 1) Received care from an outside hospital or healthcare facility (defined as receiving a life saving intervention); 2) Moribund patient with devastating injuries and expected to die within one hour of ED admission; 3) prisoners directly admitted from a correctional facility; 4) Patients requiring an emergency thoracotomy in the ED; 5) Children under the age of 15 years or under 50 kg body weight if age unknown; 6) Known pregnancy; 7) Greater than 20% total body surface area (TBSA) burns 8) suspected inhalation injury; 9) received greater than five consecutive minutes of cardiopulmonary resuscitation (CPR with chest compressions) in the pre-arrival or ED setting; 10) Known DNR prior to randomization; 11) Enrolled in a concurrent ongoing interventional, randomized clinical trial; 12) Have activated the "opt-out" process for the PROPPR trial.
Study Intervention and Duration	A protocol using the 1:1:1 (plasma:platelets:RBCs) compared to the 1:1:2 ratio. Subjects will be followed to hospital discharge or up to the 30th day of hospitalization (whichever comes first) and have a 30-day follow-up mortality assessment.
Primary Outcome Measures	Absolute percent (rather than relative percent) group difference in 24-hour and 30-day mortality (Co-primary outcomes)
Sample Size	Phase III: 580 subjects. 290 subjects/group provide 90% power to detect a difference as small as 10% in 24-hour mortality and 88% power to detect a 12% difference in 30-day mortality, assuming alpha=0.044 (adjusted from 0.05 for 3 interim efficacy analyses), two sided, and assuming 24-hour and 30-day mortality in the 1:1:1 group of 11% and 23%, respectively based on epidemiologic data. At the DSMB meeting, April 25, 2013, prior to any review of unblinded data the blinded members of the DSMB reviewed a prespecified adaptive analysis conducted by blinded ROC biostatisticians and recommended that the sample size be increased from 580 to 680 to maintain a power of >85%. NHLBI approved this modification.
Analysis	The primary clinical analyses will separately compare treatment group differences in 24-hour and 30-day mortality using Mantel-Haenszel Tests with site stratification. For Laboratory Aims 1-3 we will develop models (reverse-engineered from the laboratory data) to identify drivers and sequelae of TIC and inflammation and to assess relationships among identified phenotypes and outcomes. In addition traditional regression analyses will be conducted for Laboratory Aim 3.

Monitoring Safety	There will be three formal efficacy analyses. The 2 interim analyses for the DSMB will occur after 1/3 and 2/3 of the projected 24-hour or 30-day mortality events are observed (whichever reaches its projected 1/3 and 2/3 first). The two co-primary outcomes will be separately monitored using a two-sided O'Brien-Fleming boundary with Lan-DeMets alpha spending function based on events for each of the two comparisons. The plan for interim analysis is suggested as a guideline for the DSMB, and could be modified by the DSMB prior to the start of the trial. At each DSMB meeting after the start of the trial, we will present safety data by treatment group (labeled as A,B in the same manner proposed by the 2006 FDA Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committes, unless the DSMB requires complete unblinding). This would include, but is not limited to, total counts of all related, serious and unanticipated adverse events, including a description of the event itself. Additional safety analyses will be developed as requested by the DSMB. We will report overall mortality for the safety analysis. At the formal interim analysis we will report mortality by treatment group (or A,B).

Section 1.3 Overview of Data Collected

ASSESSMENTS	Pre ED	ED	OR	IR	Inpatient 1st 24 hrs	Inpatient Daily Assess.	Discharge Info	30 Days
Eligibility Criteria	x	x						
Demographics		x					x	
Trauma Activation	x							
EMS Care	x							
Unit arrival information		x	x	x	x			
Informed consent process		x	x	x	x	x		
Vital Signs	x	x	x	x	x	x		
Glasgow Coma Scale	x	x	x	x	x	x	x	
Extended Glasgow Outcome Score							x	
Mortality		x	x	x	x	x	x	x
Life Saving Interventions	x	x	x	x	x	x		
Injury Information	x	x						
Blood Products (including age of product)	x	x	x	x	x	x		
Non-blood Fluids	x	x	x	x	x	x		
Medications	x	x	x	x	x	x		
Surgical Procedures			x		x	x		
Interventional Radiology Procedures				x		x		
Angiogram				x				
Lab Results		x	x	x	x	x		
Hemostasis Obtained		x	x	x	x			
*Research Lab Sample Collection		x	x	x	x	x		
Multi-Organ Failure Assessment						x		
Complications					x	x	x	
Injury Severity Score (ISS)							x	
Subject Disposition							x	
Past Medical History							x	

* Research lab samples time points:
For all subjects (screened, eligible, or randomized): 0 hour
For all randomized subjects: 2, 4, 6, 12, 24, 48, and 72 hours

PROPPR Case Report Form (CRF) Guide: Randomized Patients

Case Report Form	Required for Enrolled Subjects	Considered Incomplete (all times from ED admission)
Form 1- Screening	X	72 Hours (DIRECT OBSERVATION)
Form 2 - Verification of Eligibility	X	72 Hours
Form 3 - EMS/Pre-Hospital Care	X	72 Hours
Form 4 - Randomization	X	72 Hours
Form 5 - Initial 24 hrs. Vital Signs & GCS	X	72 Hours
Form 6 - IV Fluids & Blood Products	X	72 Hours
Form 7 - End of Resuscitation/Protocol Treatment	X	72 Hours
Form 8 - Life Saving Interventions	X ●	14 Days after Discharge, Death, or Day 30
Form 9 - Procoagulant Medications	X ●	14 Days after Discharge, Death, or Day 30
Form 10 - Operating Room Visits	X ●	14 Days after Discharge, Death, or Day 30
Form 11 - Interventional Radiology Visits	X ●	14 Days after Discharge, Death, or Day 30
Form 12 - Initial 24 hrs. Clinical Lab Results	X	7 Days after Admission
Form 13 - Research Blood Sample Collection	X ●	5 Days after Admission
Form 14 - Research Blood Sample TEG/Multiplate Results	X	10 Days after Admission
Form 15 – Anesthesia Record *(Initial Resuscitation only)*	X●	7 Days After Admission
Form 16 - 24hr to 30 Day Follow-up Assessments	X ●	14 Days after Discharge, Death, or Day 30
Form 17 - Discharge/Death	X	14 Days after Discharge, Death, or Day 30
Form 18 - AE/SAE's	X ●	14 Days after Discharge, Death, or Day 30
Form 19 - Subject/LAR Contact	X ●	14 Days after Discharge, Death, or Day 30
Form 20 - Subject/LAR Consent	X ●	14 Days after Discharge, Death, or Day 30
Form 21 - End of Study	X	14 Days after Discharge, Death, or Day 30
Form 22 - Additional Information	X ●	14 Days after Discharge, Death, or Day 30
● **Required form with the option to indicate no data to report.** .		

PROPPR Case Report Form (CRF) Guide: Screen Failure Patients

Case Report Form	Required for Screening Failures	Considered Incomplete (all times from ED admission)
Form 1- Screening	X	2 Weeks
Form 2 - Verification of Eligibility	X	
Form 3 - EMS/Pre-Hospital Care	X ◘	
Form 4 - Randomization	*For Data Collection on subjects who screen out due to the 2hr time limit from ED arrival.*	
Form 12 - Initial 24 hrs. Clinical Lab Results	X ◘	
Form 14 - Research Blood Sample TEG/Multiplate Results	X ◘	
Form 22 - Additional Information	*Optional*	
Form 23 - Trauma Registry Data Form	X ●	
Form 24 - Research Blood Sample Consent/Contact Record	X ◘	
● **Required form with the option to indicate no data to report.** ◘ **Form required if research blood samples were taken.**		

Section 1.5 General Forms Instructions

General Information and Instructions for Completion of Hardcopy CRF's:

Study ID Numbers: The subject study ID number must be recorded on the upper right hand side of each CRF page. Sites will be provide with several labeling options including study ID specific PDF CRF files with barcodes on each page, blank CRF pages, and extra study ID/bar code stickers. The first 2 digits of the study ID identify the site are followed by a five digit sequential number for each subject screened and or enrolled. Study ID numbers cannot be reused once assigned to a subject.

The individual collecting the data should record their initials below the study ID number.

All data must be verifiable to a source document and all documentation needs an audit trail. Corrections on the CRF should be made using a single line strikeout with the initials and date of the individual making the correction.

The PROPPR CRF will be used as the source document for data not recorded in the subjects' medical record.

Enter all dates in dd/mmm/yy format and all times in hh:mm using a 24 hour clock format.

Print additional form pages as needed. Additional form page numbers should be added using a decimal point followed by sequential numbers. (Example: Page 5.1, 5.2, 5.2)

Use the following codes to record unknown/missing data values:
ND = Not Detectable NR = Not Recorded/Not Done NA = Not Applicable
NP = Not Palpable NK = Unknown

To accommodate the variety of units of measure for lab tests across the clinical sites, there are several places through the forms that require selection of the unit of measure for the lab test in addition to the lab value result.

The unit of measure for all blood products is units.

The unit of measure for all IV crystalloid/colloids is milliliters.

Use the following codes to record unknown/missing data values:

Paper CRF Codes		e-CRF Codes
NA	Not Applicable	-995
ND	Not Detectable	-996
NK	Unknown	-997
NR	Not Palpable	-998
NP	Not Recorded/Not Done	-999

Section 1.6 Site Certification

Purpose
To describe procedures for clinical site and HCCC/HDCC staff to follow, prior to, during, and following the initial site prior to enrollment. The purpose of the initial site visit is:

- To review with the Investigator and staff the final protocol, the Investigator's Brochure, and regulatory requirements
- To instruct study personnel in study procedures including, but not limited to patient recruitment, informed consent, randomization procedures, and Case Report Form completion.

Scope
The procedures apply to all PROPPR clinical and HCCC/HDCC staff.

References
FDA Guidance for IRBs, Clinical Investigators, and Sponsors FDA Inspection of Clinical Sponsors, June 2010
ICH Guidelines for Good Clinical Practice (E6) Section 4.2 – Adequate Resources
ICH Guidelines for Good Clinical Practice (E6) Section 4.3 – Medical Care of Trial Subjects
ICH Guidelines for Good Clinical Practice (E6) Section 4.4 – Communication with IRB/IEC
ICH Guidelines for Good Clinical Practice (E6) Section 4.5 – Compliance with Protocol
ICH Guidelines for Good Clinical Practice (E6) Section 4.6 – Investigational Products
ICH Guidelines for Good Clinical Practice (E6) Section 5.12 – Information on Investigational Products
ICH Guidelines for Good Clinical Practice (E6) Section 5.18 – Monitoring

Definitions
HCCC – Houston Clinical Coordinating Center
HDCC – Houston Data Coordinating Center
PI – Principal Investigator
HDCC PI – Data Coordinating Center Principal Investigator
E-CRF – electronic case report form
IRB - Institutional Review Board
REB - Research Ethics Board (Health Canada)

Responsibilities
HCCC and HDCC personnel are responsible for discussing in detail the type of subject/patient to be recruited, the completion of the eCRFs, administrative procedures to be followed, and the current protocol/study procedures found in the protocol and study Manual of Procedures. They are also responsible for evaluating the Investigator's and coordinator's understanding of the protocol and his/her obligations during the study, as well as, touring the facilities and confirming that all study-related clinical procedures can be completed, including blood banking and laboratory facilities.

The site PI is responsible for ensuring that his/her study team staff participates in the site visit once the scheduled date, time and location are agreed upon. For study team staff that cannot participate in site initiation, the PI shall ensure that staff receives the relevant training prior to working on the study.

Procedure
Preparation for the Site Visit:

1. The HCCC program manager will coordinate with the clinical site to schedule a date and time for the initial site visit.

2. The HDCC regulatory documents coordinator will determine which regulatory documents are outstanding and need to be requested prior to or retrieved at the site visit.
3. The HCCC program manager will send a confirmation letter outlining the purpose of the visit including demonstration of a mock randomization, and other items for discussion.
4. .The HDCC will prepare a site certification checklist to be completed before site initiation. **(Section 1.6.1)**

During the Site Initiation Visit:

1. The protocol presentation **(Section 1.6.2)** will be presented.
2. Attendance will be documented on the site visit log **(Section 16.4.2)**.
3. Obtain any missing regulatory documents (e.g., Investigator CVs and Financial Disclosure Forms) not received prior to the visit.
4. Discuss Federal requirements specified in FDA Form 1572 and IRB/REB requirements, including but not limited to:
    a. Obtaining and documenting informed consent
    b. IRB/REB approval and progress reports, including amendments and serious adverse events (SAEs)
    c. Protocol Adherence
    d. Maintenance of adequate and accurate case histories
    e. Record retention – Records must be retained for 2 years after an NDA has been approved for the stated indication, or 2 years after notification of FDA and the investigator (by the Sponsor) that the project has been completed, canceled, or discontinued, even if no NDA has been filed.
    f. Site personnel responsibility log – to document who will be responsible for specific study functions, the Delegation of Responsibilities/Authority form **(Section 16.4.1)** must be completed and signed by the PI.
5. Check that other related supplies (TEG/Multiplate, barcode readers) are available or are to be shipped to the study site at a later date, **(Section 16.4.3)**.
6. Check that the Emergency Department facility and resources are available to meet protocol requirements, e.g. level 1 trauma center, ect.
7. Check that blood banking facilities are adequate to meet protocol requirements, e.g. 24hr. staffing, emergency blood supply, etc.
8. Check that laboratory facilities and arrangements for the dispatch of samples to the laboratory are organized and that any specialized equipment that may be required will be available throughout the period of the trial, e.g. centrifuge, freezer, etc.
9. Ensure that the site PI and study coordinators understand:
    a. 24/7 staffing requirements for the study,
    b. Frequency of monitoring of subjects,
    c. Importance of obtaining primary endpoint data (24hr and 30 day mortality),
    d. Review of site certification checklist **(Section 1.6.1)** and a site specific study flow chart **(Section 1.6.3)**.

Follow-up to the Site Initiation Visit:

1. The HDCC program manager will complete and send a follow-up letter to the PI, which outlines what was accomplished during the meeting and note any items that need additional attention.
2. Place copies of the report and follow-up letter in the study file.

Section 1.6.1 Site Certification Checklist

PROPPR Site Certification Requirements Site:_____

Requirement	Completion Date
IRB/REB initial protocol approval to begin community consultation.	___/___/___
Review of site plan to obtain LAR consent, consent process for initial blood sample on screened but not enrolled subjects, and HIPAA release.	___/___/___
Completion of HDCC training session on: IRB/REB approved protocol, CRFs, completion of logs, AE/SAE reporting and adjudication process, site communication with HDCC and HCCC, site monitoring plan, monthly site performance report, protocol violation/deviation definition matrix.	___/___/___
Submission of all regulatory documents. (CV's, License, Training, COI, IRB application & approvals including protocol amendments.)	___/___/___
Completion of initial visit by HCCC and DCCC: *Tour of the following areas:* ED, blood bank, research lab (including sample processing area & freezer storage) &/or clinical lab, research offices & work area for Monitors.	___/___/___
Site completion of study flow chart.	___/___/___
Site P.I. completion of protocol update session through webinar.	___/___/___
Completion of webinar training on OpenClinica and the PROPPR SharePoint website.	___/___/___
Submission of 2 "dry-run" CRF's and screening logs in OpenClinica.	___/___/___
Completion of lab training. Collection, processing storage, shipping of research lab samples.	___/___/___
Verification study equipment & supplies. i.e.Teg/Multiplate, lab kits, mailing kits, CRF's & logs are in place & ready for enrollment.	___/___/___
Multiplate training and calibration.	___/___/___
TEG training and calibration.	___/___/___
Review of site plan for research blood sample storage/retrieval on screened subjects.	___/___/___
Verification site blood bank randomization process is in place; logs & sham process ready.	___/___/___
Review of blood transport methods to OR, IR, ICU if different than transport method to ED.	___/___/___
Review of site plan for 30 day mortality data collection.	___/___/___
IRB/REB final approval to begin enrollment.	___/___/___
Notification from PROPPR HDCC to site PI all pre-enrollment certification requirements have been satisfied, site cleared to begin enrollment.	___/___/___

Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)

Protocol Overview

Spring 2012

Objectives

- Compare the efficacy and safety of 1:1:1 to 1:1:2 transfusion ratio groups
- Co primary outcomes of 24 hour and 30 day mortality
- Comprehensively characterize trauma induced coagulation (TIC) and inflammatory milieu to give insight to phenotypes, changes over time and relationship to treatments and outcomes.

Importance of PROPPR

Since there is currently not a universally accepted massive transfusion (MT) guideline, PROPPR proposes to:

- Provide a valid, efficient clinical trial framework for in hospital trauma
- Address the survival bias in previous studies
- Reduce the risk of post transfusion complications by utilizing a predictive MT algorithm
- Contribute to evidence based guideline for MT patient treatment
- Understand the mechanisms of TIC and inflammation this will be the first to characterize the natural history of coagulopathy and inflammation.

PROPPR Study Design

- Randomized, 2 group, controlled Phase III trial
- 2 groups 1) 1:1:1 plasma:platelets:RBC ratio
  2) 1:1:2 plasma:platelets:RBC ratio
- 2 sections 1) Up to 6 month Vanguard stage
  2) Continuation stage
- Total enrollment: 580 subjects

Inclusion Criteria

1) Require the highest trauma team activation at each participating center
2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown
3) Received directly from the scene
4) Received at least one unit of blood products within the 1st hour of arrival or during pre hospital transport
5) Predicted to receive a MT by exceeding the threshold score of either the ABC score or the attending trauma physician s judgment criteria

ABC Scoring System

(2 or more points=positive prediction for MT)

- heart rate > 120 bpm 1 point
- systolic blood pressure ≤ 90 mmHg 1 point
- penetrating injury 1 point
- positive FAST exam 1 point
  (intra abdominal fluid by ultrasonography)

** if the ABC score is less than 2, the trauma attending physician, may still choose to randomize if patient is a potential MT

Exclusion Criteria

1) Received care (as defined as receiving a life saving intervention) from an outside hospital or healthcare facility
2) Moribund patient with devastating injuries and expected to die within one hour of ED admission
3) Prisoners, defined as those who have been directly admitted from a correctional facility
4) Patients requiring emergency thoracotomy in the ED
5) Children under the age of 15 years or under 50 kg body weight if age unknown
5) Known pregnancy in the ED
6) Greater than 20% total body surface area (TBSA) burns
7) Suspected inhalation injury

Exclusion Criteria Cont'd

8) Received greater than five consecutive minutes of cardiopulmonary resuscitation (CPR with chest compressions) in the pre arrival or ED setting
9) Known Do Not Resuscitate (DNR) prior to randomization
10) Enrolled in a concurrent, ongoing interventional, randomized clinical trial
11) Patients who have activated the opt out process or patients/legally authorized representatives that refuse blood products on arrival

Screening Process

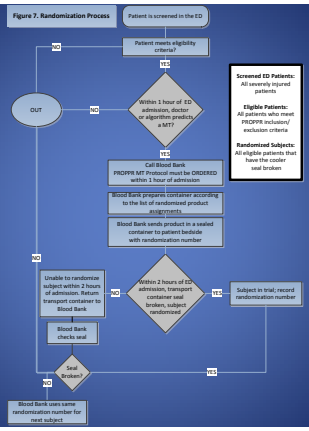
- Requires 24/7 in house research personnel coverage
- Observation & data collection begin immediately
- Research personnel will assess the ABC score

  If the score is >/= 2: patient eligible

  If the score is < 2, trauma attending can make decision if patient is predicted to be a MT
- If the score is <2 and attending says no: patient not eligible, data collection stops

Consenting Procedures

- Exception from Informed Consent (21CFR50.24)
- Community consultation required at each site
- Site's local IRB will determine method of consultation
- Opt out process determined by site's local IRB
- UT CPHS will accept site's local IRB methods
- Templates will be available for power point presentation, media release, and telephone script
- Documented informed consent will be obtained from LAR/subject
- Modified consent process for screened/not randomized pts who have only a 0 hour blood sample drawn.



Randomization

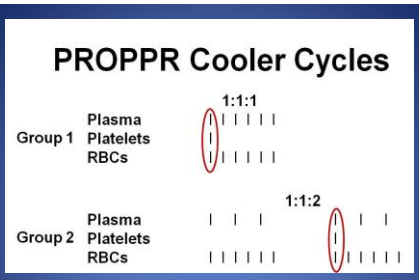
- Blood bank personnel will randomize the patient and prepare the study containers based on the ratio patient is randomized to.
- Platelets will be placed in an opaque container attached to the study container.
- The containers will be sealed.
- In the event that ABO/type specific products are unavailable, universal donor products will be used, in accordance with each blood bank s policy.
- Once seal is broken, patient is randomized/enrolled and will received products until:

  1) Hemostasis is achieved

  2) Subject has expired

  3) LAR or patient has withdrawn consent to continue in study
- If 2 patients come in at the same time and both are predicted MTs, follow only one patient.

PROPPR Cooler Cycles



- The above diagram represents one container cycle for each ratio group. Each hash mark represents one unit of blood products. Every 6 units of RBCs represent one container. The red circles indicate when platelets are given. On average, 1 unit of platelets is the equivalent of a pool of 6 units. The container cycles repeat until hemostasis is achieved.

PROPPR Definition of Adequate Hemorrhage Control

- Definition of Anatomic hemostasis
  - Surgeon declares hemostasis, based on the following objective criteria
    - No bleeding requiring intervention in the surgical field
    - In the IR suite, resolution of blush after embolization.
- Definition of when Active Resuscitation stops after anatomic hemorrhage control
  - Based on hemorrhage control criteria above, hemostasis is complete
  - Surgeon and/or anesthesiologists agree that patient is adequately resuscitated, based on the following criteria, if available:
    - Stable or increasing blood pressure, or
    - Stable or decreasing heart rate, or
    - Stable or increasing urine output, or
    - Decreasing requirement for pressors to maintain a stable blood pressure

PROPPR Definition of when Active Resuscitation Stops after Adequate Hemorrhage Control

- Actions to be taken when both anatomic and physiology criteria are met
  - Surgeon and/or anesthesiologists stops the PROPPR MT protocol (calls the blood bank and stops the transfusion)
  - All blood products and fluids received after active resuscitation stops (but within 24 hours of admission) will be recorded as post resuscitation fluid and will be given based on local practice.
- For study purposes the ratio calculation will include only the blood products transfused during active resuscitation while on protocol

Use of additional fluids/agents

The following will not be randomized or standardized but will be recorded:

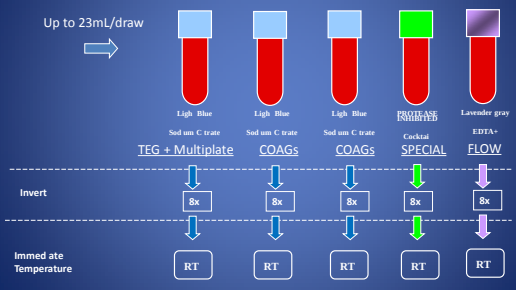
- Crystalloids
- Artificial colloids
- rFVIIa
- Amicar
- Tranexamic Acid
- PCCs
- Fibrinogen concentrates
- Cryoprecipitate

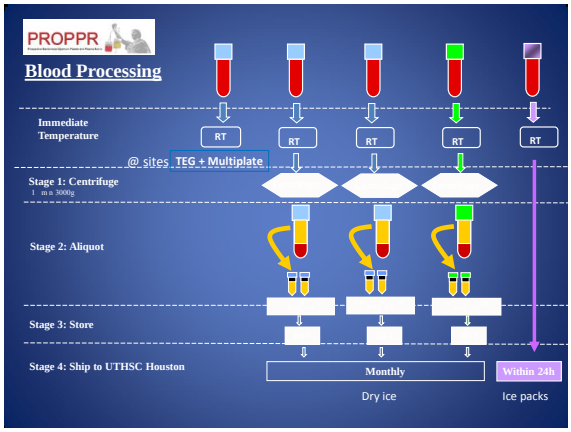
Research Sampling Plan

- Upon arrival to ED all patients receive blood draw time 0
- PROPPR enrolled patients receive additional timed draws.
- Timing 2, 4, 6, 12, 24, 48, 72 hours
- Patients not in ICU (no vascular access) excluded.
- Total 580 patients enrolled in PROPPR
  - Need to screen (first sample) 17,780

PROPPR

Research Blood Collection





Data Collection

- The research staff will do direct data collection through the initial resuscitation period up to at least the 12th hour and hourly through the first 24 hours to collect all information (fluids, procedures, etc.).
- Following the 1st 24 hours, the research staff will collect information daily while the patient is in the ICU/IMU setting and 2 times a week while on the floor until the 30th day or hospital discharge (whichever comes first).
- The 1st 24 hours of data will be submitted to the HDCC within 72 hours.
- All surviving subjects will have a 30 day follow up for mortality status details will be in the manual of operations.
- The PROPPR database will use the OpenClinica format.

Event Reporting

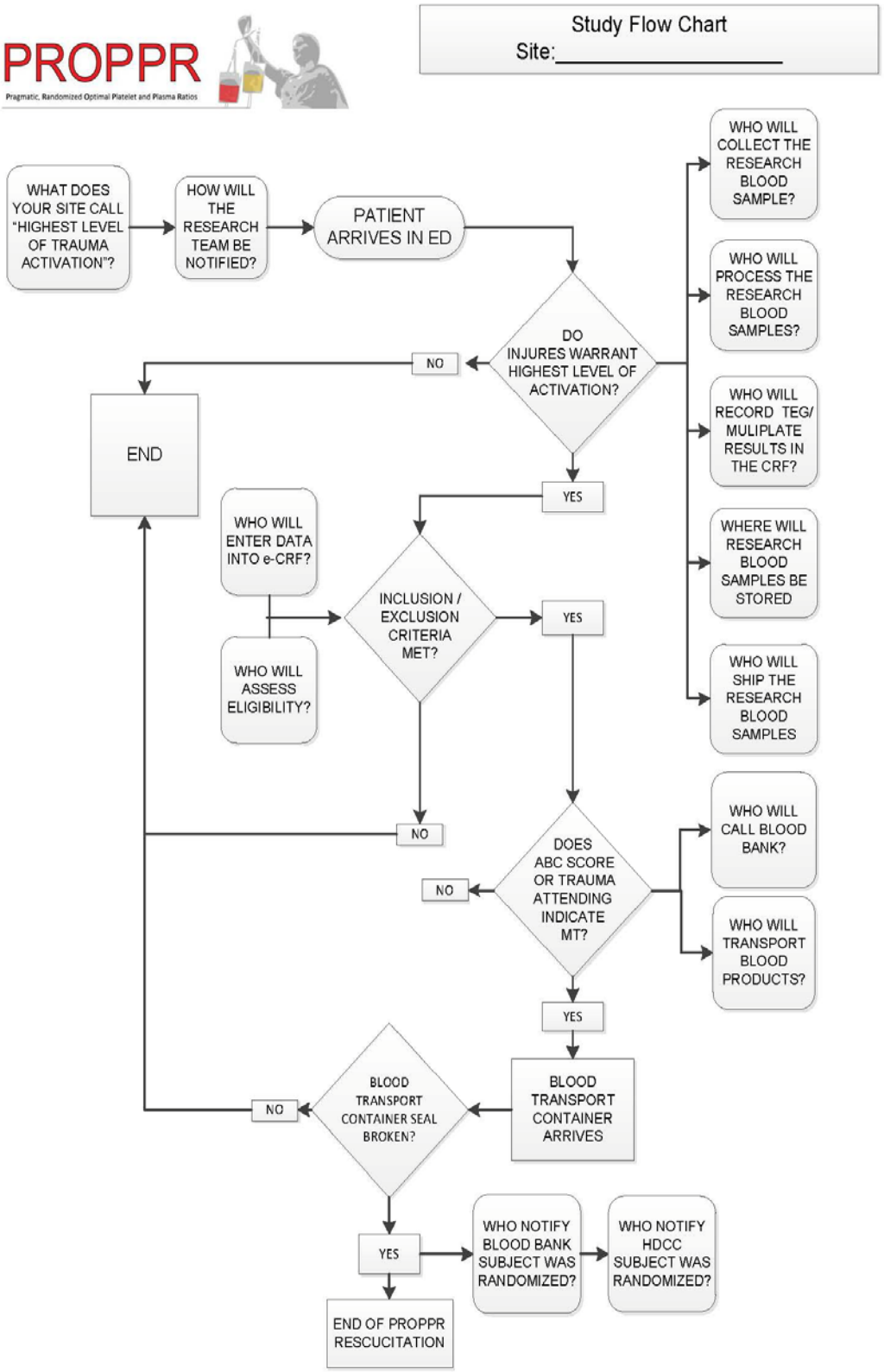
A safety monitoring plan will be provided to each site which will include a detailed list of events and the reporting requirements for each event (depending on severity and causality).

An adjudication process will be used to determine the cause of death:

The site PI will provide the cause of death, the SAE report will be reviewed by Dr. Holcomb, and difference in the causality will be reviewed by the medical monitor.

QUESTIONS?

Section 1.6.3 Site Specific Study Flow Chart Example



Section 1.7 Study Flow Diagram

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study Flow Diagram

Document Version Date: 2012 AUGUST 10

Trauma Alert!! Research team Mobilizes

RA/Coordinator Gathers CRF's, Consents, and Lab Sample Kits.

Patient Arrives in ED **(Time ZERO)**

Do Injuries Require Highest Level of Trauma Activation?

YES

Are Inclusion/ Exclusion Criteria Met?

YES

Is ABC Score ≥ 2?

NO

ABC Score < 2, Does Trauma Attending Think MT Needed?

NO

Follow Site Specific Policy for TEG/ Multiplate Analysis

HOLD TEG/Multiplate Research Blood Sample Pending Further Eligibility Assessments

NO

No Research Data or Blood Samples Collected

END

Subject Dies Before Consent From LAR is Obtained. Notification of Research Participation Letter Sent to LAR

Research Team Begins Attempts to Obtain Informed Consent from LAR/Subject → Subject or LAR Decline/Revoke Participation. Data Collection Stops. Data & Lab Samples Already Collected Will Be Retained For Analysis

Begin Data Entry into e-CRF (OpenClinica) within 72 Hours

Collect 1st Available Research Blood Sample. **HOLD** TEG/Multiplate Sample Pending ABC Score.

Blood Bank Prepares and Delivers 1st Sealed Container of Randomized Blood Products Within 10 Minutes of Notification, & Continues to Send Randomized PROPPR MT Products Until Notified to Stop

Research Team Calls Blood Bank, Notified to Randomize Subject in PROPPR MT Protocol. Randomized Blood Products Must be Ordered Within 1hr. of ED Arrival

Process Research Blood Sample for TEG/Multiplate

YES

Team Continues to Monitor Subject

Was Blood Transport Container Seal Broken Within 2 Hrs. of Arrival to ED?

NO

Lab Sample Collection STOPS

Blood Bank Notified to **Stop** PROPPR MT & Release Randomization Number, Container Returned

Blood Bank Inspects Transport Container. Seal Broken?

YES

Blood Bank Notifies Research Team Subject is IN Study

YES

Lab Sample Collection Continues/Resumes. Processed for TEG & Multiplate,Storage/Shipment

Were PROPPR MT Blood Products Given?

NO

Blood Bank Notified to STOP PROPPR MT PROTOCOL

Site Notifies HDCC of Randomized Subject

PROPPR MT Resuscitation Continues. Blood Transport Containers Returned as They are Used. Team Monitors for End of Resuscitation, Vital Signs & GCS, AE/SAE's, Clinical Lab Values, OR/IR Visits

End of Resuscitation

Begin Daily Data Collection Until Subject is Transferred Out of ICU or Monitored Unit, Then Monitor Twice Weekly Until Discharge or Day 30. Obtain HIPAA Consent Obtained (if applicable) for Follow-up After Discharge

Provide Enrollment Updates to HDCC

Follow AE/SAE Reporting Procedures

Respond To Data Queries

Subject Remains Hospitalized on Day 30?

NO

For Subjects Discharge Before Day 30: Contact for Vital Status. Query Death Registries if Unable to Make Contact. Enter Final Data in OpenClinica

YES

Collect Final Assessments for Subjects Still Hospitalized on Day 30. Enter Final Data in OpenClinica

Follow Local IRB Policy For 1st Available Blood Sample Consent

Subject is Considered a **Screening Failure**

NO

Data Collection **Stops** at the Point Patient is Determined Ineligible. Reason for Ineligibility and Demographic Information Entered Into e-CRF

TIME ZERO

Subject MUST Receive 1 Unit of Blood Product Either Pre-Admission OR Within 1 Hour After Arrival to ED, BUT NO MORE Than 3 Units of RBC's to be Randomized.

Blood Products Seal Must be Broken Within 2 Hours After Arrival

24 Hour Mortality Assessment

30 Day Mortality Assessment

1st AVAILABLE BLOOD SAMPLE | 2HR BLOOD SAMPLE | 4HR BLOOD SAMPLE | 6HR BLOOD SAMPLE | 12HR BLOOD SAMPLE | 24HR BLOOD SAMPLE | 48HR BLOOD SAMPLE | 72HR BLOOD SAMPLE

Chapter 2 Recruitment and Patient Consent

Section 2.1 Patient Population

The target population is trauma subjects who are admitted to one of the participating sites and who meet the inclusion and exclusion criteria detailed below.

This trial qualifies for the "Exception from informed consent required for emergency research" outlined in the FDA regulation 21CFR50.24 as follows:

1. Subjects are in a life-threatening situation and collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular interventions
2. Obtaining informed consent is not feasible because the subject cannot give reasonable consent due to medical condition, intervention must be given before consent can be obtained from a LAR, and cannot prospectively select subject
3. There is prospect of direct benefit to subject because they are in a life-threatening situation requiring intervention, risks associated with this study are reasonable compared to standard of care therapy
4. The research could not practically be carried out without a waiver
5. Diligent attempts will be made to contact the LAR or family member for them to object to subject's continued study participation within the protocol-defined therapeutic window of the first 20 minutes and for the 24-hour study treatment duration
6. IRB has reviewed and approved the informed consent procedures and documents to be used with the subjects or LAR for this study.
7. Additional protection of rights will be provided which will include: community consultation and public notification, an established independent data safety monitoring committee, and efforts will be made to obtain informed consent from family members if the LAR is not available.

Section 2.2 Community Consultation

Public notification and community consultation in accordance with local IRB and Canadian REB policies will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions, it will not be possible to target specific individuals although the local IRB/REB may recommend targeting specific groups. The community consultation plan for each trial site will be individualized to fit the IRB/REB requirements. The participating sites have considerable experience conducting community consultation. A variety of methods are employed including consultation with community leaders and targeted community groups, random telephone surveys, and community meetings.

Visual aids, such as power point, flyers or posters can be used in the presentations, and all material will be in lay terminology. Each communication will include information as to the purpose of the trial, the consent process, the risk and benefits to the community/patient, and the time commitment required. As each community is unique and may require specific or special needs, the local IRBs/REBs will approve the methods for their community and ensure that community consultation practices are both appropriate and complete before consent is given to begin the trial.

During the course of public notification/community consultation, including public advertising of the study, individuals in the community not wishing to be enrolled in the trial will be provided opportunity to "opt out" in advance for treatment. Those contacting a published address and /or telephone number for the investigators will be given a bracelet or its equivalent without cost which, when displayed, indicates ineligibility for the study. A letter will accompany the bracelet/item indicating that it must be displayed on person in a recognizable manner in order to be identified by providers. Providers will be trained to recognize such bracelets or their equivalent, and that the identification of such an item would exclude the patient from trial enrollment.

Section 2.2.1 Community Consultation Templates

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

(PROPPR)

[SITE NAME] Community Consultation

[SITE PI NAME]
[SITE Name, Department, Clinical Institution Name]

Sponsored by National Heart Lung and Blood Institute (NHLBI), National Institutes for Health (NIH)

What is Trauma?

- Refers to a "a body wound or shock produced by sudden physical INJURY, as from violence or accidents.
- Leading cause of death in people under the age of 45 years old.
- People who have suffered trauma may require specialized care, including BLOOD TRANSFUSIONS and SURGERY.

Background

- Nearly 50% of trauma deaths occur before the patient reaches the hospital and few of these deaths are preventable.
- For those that reach the hospital, about 40% experience bleeding complications and require a MT (massive transfusion of at least 10 units of blood)
- Bleeding complications are the leading cause of early death in trauma patients.

Background

- Current military transfusion guidelines for massively transfused casualties are based on the U.S. Army Surgeons General recommendation of a 1:1:1 ratio.
- Studies in both the public and military populations have shown that seriously injured patients who received a massive transfusion (MT) with higher plasma ratios had lower mortality than those who received more traditional ratios of plasma.
- Question remains: What is the best ratio group to use for trauma patients who require a large amount of blood?

What is the PROPPR study?

- This study involves research.
- Multi-center study including at least 12 North American Level 1 trauma center sites.
- Purpose: Determine what the best ratio of products is to provide the best outcomes for the patients.
- Plan: Enroll patients who are PREDICTED to receive significant amounts of blood products into a protocol using 1:1:1 ratios of plasma to platelets to red blood cells (RBCs), compared to 1:1:2
- The knowledge gained will likely impact the way in which massively bleeding patients are transfused and lower the amount of otherwise preventable deaths resulting from hemorrhagic shock

What Are Red Blood Cells, Platelets, Plasma

- Red Blood Cells are cells that carry oxygen
- Platelets are the smallest structures in the blood and are important for blood clotting and plugging damaged blood vessels.
- Plasma is the liquid portion of the blood; represents approximately 50% of the total volume of blood and contains coagulation proteins

Patient Selection

Inclusion

- Severely injured
- Estimated age 15 years or older or greater than/equal to weight of 50 kg if age unknown
- Received directly from scene of injury
- Received at least one unit of blood product products within the first two hours of injury
- Predicted to receive a massive transfusion by scoring system or the attending trauma surgeon's judgment

Exclusion

- Received care from outside hospital
- Non-survivable injuries
- Prisoners directly admitted from jail
- Required emergency thoracotomy
- Children less than 15 years or less than 50 kg body weight if age unknown
- Obvious pregnancy
- Severely burned
- Had at least 5 minutes of CPR with chest compressions before admission
- Known "Do Not Resuscitate" orders prior to randomization
- Enrolled in a concurrent ongoing interventional, randomized clinical trial
- Patients who wear "opt-out" bracelet
- Religious objections to blood transfusions

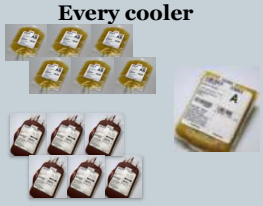
How are patients selected for this study?

- The trauma physician on call in the emergency department will use information obtained when a patient first arrives to predict if he/she will require a significant amount of blood products. The information includes blood pressure, pulse, type of injury, and an ultrasound test to see if there is bleeding in the abdomen (FAST exam).
- For patients who are eligible for this study, the blood bank will be notified to randomize (a process like flipping a coin) the patient to receive one of two ratio groups (either 1:1:1 or 1:1:2).
- The study blood products will be given ONLY in the initial 24 hours.

What about other treatments and care?

- People enrolled in this study will continue to receive all other treatments and care they would have received anyway. If you are not in the study, the only difference would be that the combination of blood products given would be decided by the physicians and not by the study randomization.

How will the PROPPR transfusion be given?

Group 1 1:1 Ratio	Group 2 1:2 Ratio
Every cooler	Every other cooler
	

Is the blood safe?

- All blood products we use will be processed through [site's blood bank name]
- All blood products are approved by the U.S. Food and Drug Administration (FDA) and the American Association of Blood Banks (AABB), and/or Health Canada
- All blood products are typed and crossed
- All blood products will be tested for infectious diseases
- All hospitals have established policies and procedures to safely transfuse blood products

What will be studied?

- We will collect blood samples upon arrival and up to 72 hrs
  - Time points: at 0, 2, 4, 6, 12, 24, 48, and 72 hours (or discharge from hospital – whichever occurs first)
  - Up to a total of 23 cc of blood will be collected at each time point for research purposes
- Daily medical record will be reviewed
- The 0 hour sample will be collected on all potential patients and stored for future tests which WILL NOT include genetic testing with the patient's approval.
- The patient will be contacted by the study team near the 30th day following the emergency department admission to find out how they are doing on day 30

Any Risks?

- You would have these risks whether or not you were in the study but it is unknown at this time whether these risks (for example, lung injury) are more severe or last longer when one unit of red blood cells is administered for every unit of platelets and plasma compared with two units of red blood cells administered for every unit of platelets and plasma
- Risks include: chance of transmission of an infectious disease, low blood pressure, allergic reaction, shortness of breath, fever, blood clotting problems

What is the informed consent process?

- The consent process is when we ask a person's permission and invite him/her to be in a study, explaining the risks and benefits, as well as answering any questions
- Patients will be unable to consent
- People will be entered into the study without providing informed consent
- Every attempt will be made to obtain consent from the legal representative and/or family member to join or continue with the study or to refuse to allow the patient to join or continue in the study
- Enrolled patients will be informed of study when able and will be allowed

INFORMATION YOU SHOULD KNOW

- Patients and/or their family members/legal representatives can decide at any time to withdraw from a study
- Patients will receive the same care whether they are not they are in the study
- There is no extra cost for being in the study; the patient will not receive compensation for being in the study
- If an injury occurs which is related to the study, the patient will not receive compensation for the injury and medical care will be available just as it is to the general community

INFORMATION YOU SHOULD KNOW

- Every effort will be made to ensure patient privacy
- All data reviewed for the purposes of this study will be de-identified-personal identification such as name, medical record number will be removed
- The FDA may inspect the records at any time
- Members of the community may "opt-out" if they do not wish to be in the study. A colored, plastic bracelet with the word "PROPPR Ø" on it will be available for those who **DO NOT** want to be considered for this study. If a patient arrives to the ED with this bracelet on, they will not be screened or enrolled in this study

Questions?

- For questions pertaining to this study:
  Local PI Name and contact information
- For questions pertaining to informed consent:
  Local Site IRB name and contact information
- If you would like to "opt out" of the study:
  Local PI Name and contact information

THANK YOU

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

COMMUNITY CONSULTATION

Organization: _____

Date: _____

Please circle your answers.

1. Will you allow us to conduct a research study in this community of people experiencing a major traumatic event requiring multiple blood transfusions who are unable to give their own informed consent?
   YES NO
2. If you were involved in a major trauma event and needed many blood transfusions, would you want to be enrolled in this type of study?
   YES NO
3. If a close friend or family member of yours was involved in a major traumatic event requiring a massive blood transfusion, would you want him/her to be enrolled in this type of study?
   YES NO

Are there any questions or concerns you would like to let the investigator know about?
Please write here:

_____

_____

Age: _____ Ethnic Background: _____

Gender (circle one): Male Female

For additional questions and/or concerns, please feel free to contact _____

_____ with the ***[Institution's IRB / Humans Subjects Protection Committee]*** at ***[Phone Number].***

WE THANK YOU FOR YOUR PARTICIPATION TODAY!!

Random Digit Dialing Telephone Script Template

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Telephone Script for

Community Consultation

Hello, my name is _____, and I'm a research assistant at ***[Institution Name]***. This call does not involve sales of any kind. We are currently conducting a survey on behalf of ***[Institution Name and Medical Center]*** to obtain community opinions and views on a medical research study involving severely injured patients. The ***[Institution's Name and Hospital / Medical Center]*** will be using your opinions to help determine whether the study is acceptable to the community. Your answers will be confidential.

The survey will take approximately 10 minutes of your time, during which I will describe the study to you and ask for your opinions about it. I will also ask you a few questions about yourself. You do not have to answer any questions you do not want to, and you may stop the survey at any time.

Would you be willing to offer your opinions and answer some questions about yourself after I give you details about the study?
[If YES then continue, if NO, say thank you for your time]

Are you eighteen years old or older?
[If YES, continue--- if NO, ask to speak to someone 18 years old or older; reintroduce yourself with paragraph 1] Thank you!

---[READ THE FOLLOWING PRIOR TO ASKING SURVEY QUESTIONS]---

A study comparing ways to give blood transfusions is being proposed in patients with severe injuries, like those that can occur in bad car accidents, who have a significant chance of dying from their injuries and blood loss. Usually, patients are told about a study, its risks, and its potential benefits, and then they provide a written consent. However, in the case of severe injury, it is not always possible for patients to give written consent because they may be unconscious, and their families may not always be available to speak for them.

The U.S. Food and Drug Administration allows for certain studies to be performed without obtaining written consent in emergency settings, but only if patients have a high risk of dying without treatment, cannot communicate because of their condition, and don't have family available to speak for them. Patients may be enrolled in this research only if **discussed** in the community in advance. We would like your opinion on our proposed study which involves severely injured patients. **First, I will give you information about the study and then I will ask**

you for your opinion.

Trauma refers to a "body wound or shock" produced by sudden physical injury, as from violence or accidents. Trauma injuries are the leading cause of death in people under the age of 45 years old, and nearly 50% of these deaths occur before the patient reaches the hospital. For those that reach the hospital, about 40% experience severe bleeding and require a massive transfusion of at least 10 units of blood. Bleeding complications is the leading cause of **early** death in trauma patients. People who have suffered trauma may require specialized care, including blood transfusions and surgery.

The purpose of this study is to help determine which blood transfusion combination will provide the best outcomes for the trauma patients receiving them. In addition to ***[City Name],*** we are proposing to conduct this multi-center study at other Trauma Centers across the U.S. and Canada.

The knowledge we gain will likely impact the way in which patients who are severely bleeding are transfused, and lower the amount of otherwise preventable deaths resulting from hemorrhagic shock. The trauma surgeon on call in the emergency department will use information obtained when a patient arrives to the emergency department to predict if the patient will require a significant amount of blood products. The information includes their blood pressure, pulse, type of injury, and an ultrasound test to see if they are bleeding in the abdomen.

For patients that are eligible for this study, the blood bank will be notified to randomize (a process like flipping a coin) the patient to receive one of two blood combination groups -- one that gives more plasma and platelets and one that gives less.

All other treatments will be the same.

All blood products we use will be just like the normal products patients get for transfusions, and all blood products are approved by the U.S. Food and Drug Administration and the American Association of Blood Banks**[, and Health Canada].** All blood is typed, and will be tested for infectious diseases. This is the standard practice if you receive a blood transfusion. As with any blood transfusion, there are risks involved, which include chance of transmission of an infectious disease, low blood pressure, allergic reaction, shortness of breath, fever, and blood clotting problems.

-Patients and/or family members/legal representatives can decide at any time to withdraw from the study.
-Patients will receive the same care whether or not they are in the study. The patient will only receive blood products if the physician determines they need the blood. The patient will not receive extra blood products because of the study.
-There is no extra cost for being in the study.
-Every effort will be made to ensure patient privacy.

-All information reviewed for the purposes of this study will be made anonymous.

If anyone in the community does not wish to take part in this type of study, they can call a special number to request an "opt out" bracelet or identification card (ID card) that would notify Emergency Medical personnel that they do not wish to be enrolled. The "opt out" bracelet is a colored, plastic bracelet with the word "PROPPR Ø" on it will be available for those who **DO NOT** want to be considered for this study. The ID card will be about the size of a driver's license or credit card with the word "PROPPR Ø" on it. If a patient arrives to the ED with this bracelet on, they will not be screened or enrolled in this study

As I mentioned before, we called to speak to you today because patients who are eligible for the study will be unable to consent and will be entered into the study without providing informed consent. We will make every attempt to get consent from their legal representative and/or family member, and will inform patients about the study as soon as we are able.

We would like to ask you some questions about your opinion on this.

1. Based on the information I just read to you, do you understand what this study is about?
a. Yes
b. No
c. Don't know
d. Refused

2. At any moment, we are all at risk of serious injury, especially in an automobile. If you were severely injured and it was determined that you would need blood products, would you find it acceptable to be enrolled in this study without written consent?
a. Yes
b. No
c. Don't know
d. Refused

3. Do you believe that this exception to written consent is justified?
a. Yes
b. No*
c. Don't know
d. Refused
* If NO: What is your reason for concern? _____
_____

4. Do you believe the research is in the best interest of the patients and community?
a. Yes
b. No*
c. Don't know
d. Refused

* If NO: What is your reason for concern? _____
_____

5. Why do you feel this exception to consent is justified?
a. It is in the best interest of the patient
b. It is in the best interest of the community
c. It is in the best interests of both the patient and the community
d. Don't know
e. Refused
f. Other: _____

6. Injury is the leading cause of death in teenagers, ages 15-18 years, and because they have the same risk and benefits with the transfusion ratios as adults, do you think it is appropriate to include 15-18 year old children in this study?
a. Yes
b. No*
c. Don't know
d. Refused
* If NO: Please tell me why? _____
_____

7. Do you have any additional comments about giving this experimental transfusion ratio without written consent by the patient? [*Record verbatim*]

_____
_____
_____
_____
_____
_____

If you would like more information regarding the study, I can give you a name and number for the local study coordinator or you can visit the study's website address, would you like any of that information?

Local Study Coordinator Name _____

Local Site number_____

Website: http://www.uth.tmc.edu/cetir/PROPPR/index.html

We thank you for your time so far. The following questions are only to make sure that we have a representative sampling of our community's opinions. Your answers will be kept confidential.

8. What is your age? _____

9. Are you the parent or legal guardian of a child or children ages 15-18 years old?

_____

10a. What is your race? [*Record one response*]
a. Caucasian/White
b. African American/Black
c. Asian
d. Hispanic
e. American Indian/Native American
f. Mixed Race
g. Other [SPECIFY]_____
h. Don't know
i. Refused

10b. What is your ethnicity? _____

11. What is the highest level of education you have completed?
a. Less than 9th grade
b. 9th to 12th grade- no diploma
c. High School graduate/ Equivalency (GED)
c. Associate, Technical or Vocational degree
d. Bachelor's degree
e. Post-graduate degree
f. Refused

12. What is your occupation? _____

13. What is the zip code where you live? _____

14. What is your approximate annual household income? _____

-This concludes our survey. We thank you very much for your time!-

Citizen's gender:

1. Male 2. Female

_____

Interviewer Name **Date**

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

PUBLIC NOTIFICATION: Research Project for Blood Transfusions in Trauma Patients Seeks Community Input

Researchers at **[Institution]** are launching a new research study to find the best way to give blood transfusions for severely injured patients predicted to require massive blood transfusions upon arrival to the **[Name of Hospital]** emergency department. **[Principal Investigator, M.D.], with/at** the **[Department/Institution],** is principal investigator for this clinical study.

The purpose of this study is to help determine which blood transfusion combination will provide the best outcomes for the trauma patients receiving them. The two blood transfusion combinations which are a) 1 unit of red blood cells: 1 unit of plasma:1 unit of platelets compared to b) 2 units of red blood cells: 1 unit of plasma: 1 unit of platelets. Both combinations are in widespread use across the United States. This study will be conducted at 12 Level 1 trauma centers across the United States and Canada. Dr. **[PI]** and **his/her** team will be a part of this research team which will look at the resulting information to see if using one combination of blood products or the other can possibly increase the chances of survival and reduce complications.

The knowledge gained will likely impact the way in which patients who are severely bleeding are transfused, and lower the amount of otherwise preventable deaths resulting from hemorrhagic shock. The trauma surgeon on call in the emergency department will use information obtained when a patient arrives to the emergency department to predict if the patient will require a significant amount of blood products. The information includes their blood pressure, pulse, type of injury, and an ultrasound test to see if they are bleeding in the abdomen. For patients that are eligible for this study, the blood bank will be notified to randomize (a process like flipping a coin) the patient to receive one of two blood combination groups -- one that gives more plasma and platelets and one that gives less. This is the investigational (or research) part of the study. All other treatments will be the same. If a patient is not in the study, the amount and type of blood products they receive will be decided by the trauma physicians, not by the randomization process for this study.

All blood products we use will be just like the normal products patients get for transfusions, and all blood products are approved by the U.S. Food and Drug Administration (FDA) and the American Association of Blood Banks (AABB) and Health Canada. All blood is typed, and will be tested for infectious diseases. This is the standard practice if you receive a blood transfusion. **[Name of Hospital]** has policies and procedures established to safely transfuse blood products.

As with any blood transfusion, there are risks involved, which include chance of transmission of an infectious disease, low blood pressure, allergic reaction, shortness of breath, fever, and blood clotting problems however it is unknown at this time whether these risks are more severe or last longer (for example, lung injury) when one unit of red blood cells is administered for every unit of plasma and platelets compared with two units of red blood cells given with every unit of plasma and platelets.

The trauma physician will enroll incoming patients who are good candidates for this study. This study will require the physicians to begin experimental emergency treatment without first obtaining informed consent of the patient or a legal representative and/or family member. All reasonable attempts will be made to contact a family member to discuss this study and obtain their permission for the patient to be in the study. The patient and/or family members can decide at any time to withdraw from the study if they choose. Patients who are enrolled in this study will be closely monitored for the first 24 hours they are in the hospital, frequently during the in hospital stay and contacted after 30 days (if they have been discharged from the hospital) to follow up on how they are doing.
Patients who do not wish to be in this type of study will be given options for opting out. Anyone who does not wish to be involved in this study should contact [Site Contact Name] at [Site Contact's Number] and ask for an "opt out" bracelet to be sent to them. The "Opt Out" bracelet is a colored, plastic bracelet with the word "PROPPR " on it. If a person has this bracelet on when they arrive to the emergency department needing treatment, they will not be screened or enrolled into this study.

[PI] and members of the research team will present the project and field questions at a series of meetings with a variety of groups depicted as representatives of **[City, County],** and surrounding cities and counties. A member of the **[Name of IRB]** will also attend the meetings to assist in answering any questions related to emergency consent issues, etc. Upon completion of the community consultation meetings, **[PI]**'s team will report back to **[Name of IRB],** which will determine whether **[Institution]** will participate in this clinical trial.

If you would like to schedule a community consultation meeting or would like more information, please contact **[Site Contact Name]** at **[Site Contact's Number].**

Section 2.3 Informed Consent Development and Management

Purpose

The purpose of the document is to outline the procedures involved in development of the informed consent form templates and the subsequent review, tracking, and management of site specific IRB/REB approved consent forms utilized in the PROPPR clinical trial.

Scope

This document includes information on the development and distribution of the ICF template by the HCCC/HDCC, the review and approval process which takes place prior to site IRB/REB submissions, and the process for tracking and managing consent forms after clinical site IRB/REB approval.

References

21 CFR Part 50 Protection of Human Subjects; 21 CFR Part 50, subpart 50.25 Elements of Informed Consent
FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research
FDA Guidance on Research Involving Coded Private Information or Biological Specimens, October 2008

Definitions

ICF- Informed consent form
IRB- Institutional Review board
DSMB- Data safety monitoring board
FDA- Food and Drug Administration
HCCC – Houston Clinical Coordinating Center
HDCC- Houston Data Coordinating Center
PI – Principle Investigator
REB – Research Ethics Board
ROC – Resuscitation Outcomes Consortium

Responsibilities

The HCCC/HDCC is responsible for:

- Development and modification of the PROPPR informed consent templates
- Distribution of the informed consent templates
- Ensuring that any clinical site IRB/REB-required modifications do not alter the spirit or meaning of the ICF template language

Note: The content of the consent templates are agreed upon by the HCCC/HDCC PI's and co-investigators to ensure that all appropriate risk information is included.

The clinical site PI and/or research coordinator is responsible for:

- Modifying the ICF templates to meet local IRB/REB requirements, if indicated, and notifying the HCCC/HDCC of modifications to ensure essential required template content remains intact during the submission process

Procedures

0.1 ICF Development and Distribution

- Template ICFs are developed by the HCCC/HDCC based on the current PROPPR protocol.
- The ROC, DSMB and FDA, and Health Canada will be provided copies of the ICF templates for reference and approval.
- Templates will be submitted to the UT Coordinating Center IRB for review and approval.
- The UT Coordinating Center IRB/REB-approved Template ICFs will be distributed to participating clinical sites for the purpose of developing a comprehensive document that includes both the template language and any site-specific wording provided by the local IRB/REB. The final document should be an accurate portrayal of the risks of the research, which can be comprehended at a 6-8th grade reading level.
- Template elements that must be included in the ICF are as follows:
  - Name of Study
  - Name of Sponsor (Funding-NHLBI and/or Health Canada for Toronto site)
  - Name of Investigator and Contact Information
  - Name of IRB and Contact Information
  - Number of subjects to be enrolled (also number at the local site)
  - Clear description of the purpose of the research
  - Statement that participation is voluntary (also indicate how research differs from usual care)
  - Description in lay terms of what can be expected of the subject (including time commitment)
  - Indication of which procedures are not approved by the FDA
  - Description of randomization and what that means
  - Listing of all risks associated with each procedure
  - Indication of what is expected of the patient
  - Indication of who is responsible for any medical coverages
  - Notification that there may be no direct benefit from participating
  - Notification that there is no compensation for participating
  - Who will have access to the patient's information
  - Who the patient should contact in the event of study related injury
  - Signature lines with date/time for patient or LAR, and study personnel obtaining consent.

0.2 Site-specific ICF Review and Approval by the HCCC/HDCC

- Upon receipt of s site specific modified ICF, the HDCC regulatory documents coordinator will promptly review the consent for the following:
  - Does the ICF include all of the elements above?
  - Does the ICF include all risks related to participating in the research?
  - Does the ICF include any site specific language that is at odds with the Coordinating Center approved ICF template?
  - Is the ICF readable (e.g. language, grammar, spelling, etc.)
  - Is appropriate HIPAA language included?

0.3 ICF Tracking

- Clinical site research coordinators will provide the HDCC regulatory documents coordinator with all subsequent site IRB/REB approved ICF's submitted for continuing review or associated with protocol amendments. The HDCC regulatory documents coordinator will log this information into the PROPPR regulatory database for site metrics reporting and monitoring purposes as detained in chapters 12 and 15 of this manual.

Legally Authorized Representative/Subject Informed Consent Template To Join the Study

Pragmatic randomized Optimal Platelet and Plasma Ratios
(PROPPR)

INFORMED CONSENT TO JOIN A RESEARCH STUDY

INVITATION TO TAKE PART:

You are being asked to enroll in this research study because you will require blood transfusions due to a life threatening injury. This research study is called, "Pragmatic, Randomized Optimal Platelet and Plasma Ratios," conducted by **[insert local PI name]** at **[insert local site name]**. For this research study **he/she** will be called the Principal Investigator or PI.

Your decision to take part in this study is voluntary and you may stop taking part in the study at any time. A decision to not take part in the research study will not change the services available to you from **[insert local PI name]** at **[insert local site name]**.

You may refuse to answer any questions asked or written on any forms.

DESCRIPTION OF RESEARCH:

PURPOSE:

The purpose of this study is to determine which combination of blood products given to trauma patients will improve survival. Blood contains many types of specialized cells flowing in liquid called plasma. *Red blood cells*, or RBCs, carry oxygen throughout the body. Cells called *platelets* have an important role in stopping bleeding after an injury. *Plasma* is mostly made up of water and carries around the RBCs and platelets.

RBCs, plasma, and platelets are routinely given to patients who have experienced significant blood loss, but the best way to combine them for a patient who is bleeding is unknown. A "*unit*" refers to a bag of transfused RBCs, plasma, or platelets. The combination of blood products given to patients varies significantly. This research study will compare patient responses to 2 different combinations of RBCs, plasma, and platelets in common use

This study is being conducted in at least 12 different trauma centers in the US and Canada. A total of 680 subjects will participate across all sites. This location will enroll approximately **[insert #]** subjects. The National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), and Defence Research and Development Canada, are paying for this study to be completed.

PROCEDURES:

If you are eligible to take part in this research study, you will receive one of 2 combinations of RBCs, plasma, and platelets, and will have blood samples collected for study purposes. If you decide to join and stay in the research study, it will be necessary to collect more blood samples,

and continue collecting information from your medical record. You can get out of the study at any time.

The research study involves the following sequence of events and procedures. A member of the research team will let you know what study procedures, if any, have already been done.

1. A trauma surgeon decided that blood transfusions are needed.
2. A member of the research team confirms study eligibility, and will randomly assign (like the flip of a coin) you into 1 of 2 groups;
   - **One unit of red blood cells for every unit of platelets and plasma**
     - **OR**
   - **Two units of red blood cells for every unit of platelets and plasma**
3. Blood samples (about 2 tablespoons each), will be collected at the time of arrival to the trauma center, and 2, 4, 6, 12, 24, 48, and at 72 hours after arrival (if still hospitalized). The blood samples drawn for this study will be used to look at 1) how your body has reacted to the injury, 2) how your blood is clotting (or clumping together) and 3) how your body has reacted to the fluids and treatments you received.
4. Information will be collected regarding the injury and the care received until you are discharged from the hospital or for the first 30 days of your hospital stay (whichever comes first). The information collected will include medical history, lab values, surgery reports, vital signs (ex. blood pressure, heart and respiratory rate, and temperature) x-rays, and medicines you are taking. We collect this information to see how you are doing while you are in this study. We will check to see when you leave the hospital. If you leave **[name of hospital]** before day 30 after your injury we will, with your permission, call you to ask you how you are doing. If you were transferred to another hospital setting, we will ask for your permission to contact that facility to follow up on your progress. You will need to sign an additional HIPAA form to allow us permission to contact the other hospital and get your medical information. We will ask if you have experienced any problems since leaving the hospital. You have the right to refuse to answer any of the questions.

You will receive all other standard of care treatments for your trauma injuries and will only be enrolled in this protocol if predicted that you require a massive transfusion. Although you will be randomly assigned to receive one of two combinations of blood products, the amount of blood given to you will be based on your medical needs. Also, when the blood transfusions will be stopped will be based on your medical needs.

BENEFITS:

You may receive no direct benefit from being in this study; however, your taking part may help severely injured patients get better care in the future.

RISKS AND/OR DISCOMFORTS:

The transfusion of any blood product carries a small risk of transmission of hepatitis, HIV (the virus that causes acquired immune deficiency syndrome, or AIDS), and other viral and infectious diseases, hypotension (low blood pressure), allergic reactions, shortness of breath, blood clotting

complications, hypoventilation (too little air entering the lungs) and fever. Hospitals have established policies and procedures to safely transfuse blood products. You will have these risks, because of the blood transfusion you will receive to treat your injury, whether or not you are in the study.

All the blood products used will be processed through **[site's blood bank name]**. All the blood products are approved by the U.S. Food and Drug Administration (FDA) and the American Association of Blood Banks (AABB) and/or Health Canada. All the blood given is typed and will be tested for infectious diseases. Hospitals have established policies and procedures to safely transfuse blood products. You would have these risks whether or not you were in the study but it is unknown at this time whether these risks are more severe or last longer (for example, lung injury) when one unit of red blood cells is administered for every unit of platelets and plasma compared with two units of red blood cells administered for every unit of platelets and plasma."

Possible risks with the blood collection include localized pain from the needle stick, swelling, and redness. Patients routinely have an intravenous (IV) catheter or tube inserted into a vein for the first few days after a major injury to provide fluids and medications. The research team will avoid additional needlesticks to patients whenever possible by collecting blood samples from existing IV catheters or during blood draws for other lab tests.

Another possible risk is a breach of confidentiality. Measures in place to protect confidentiality include the use of study numbers on blood samples and study records instead of patient names, and the use of password protected computers and encrypted databases. Electronic data will be stored on protected servers. Study records will be stored in locked file cabinets within locked offices.

ALTERNATIVES:

The alternative to being in this study is for you to receive the standard of care for transfusion of blood products per local hospital policy.

STUDY WITHDRAWAL:

You can take yourself out of this study at any time without penalty and without affecting your future medical care at this center. If you choose to withdraw within the first 24 hours of treatment, you will be switched to routine blood transfusion therapy. The research team may also remove you from the study if they feel it is not in your best interest to continue taking part. If you decide to stop taking part in the study, no additional study procedures will be performed and no further information will be collected. The information collected up to the time you chose to stop being in the study will remain in the research database and will be included in the data analysis.

IN CASE OF INJURY:

If you suffer any injury as a result of this study, please understand that nothing has been arranged to provide free treatment at **[insert site name]** or any other type of payment. However, all facilities, emergency treatment and professional services will be available to you use just as they

are to the community in general. Please report any injury to **[insert PI name]** at **[insert PI contact number]** and **[if applicable, insert local IRB contact telephone number]**. You will not give up any of your legal rights by signing this consent form.

COST, COMPENSATION, and REIMBURSEMENT:

There are no additional costs for taking part in this study. You or your insurance will be responsible for all standard-of-care charges including the blood transfusions that are routinely given to trauma patients. You will not be charged for lab tests performed strictly for research purposes.

There will be no payment to you for taking part in this research study.

If you received a bill that you believe is related to your taking part in this research study, please contact **[insert PI name]** at **[insert PI contact number]** with questions.

CONFIDENTIALITY:

Please understand that representatives of the Food and Drug Administration (FDA), the **[insert local IRB name]**, the UTHouston Data Coordinating Center (HDCC), NHLBI, NIH, and Defence Research and Development Canada, may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. Your research records will be kept **at [insert local institution name]** for **[# years]** per **[name of institution]** policy.

There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information.

(OR use the wording below for sites which include the HIPAA language in this form)

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires **[use either "your health care provider" or the actual name of the entity holding the health records]** to obtain your permission for the research team to access or create protected health information about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you relative, as described in this document, for purposes of this research study **[if applicable, add: and for your treatment]**. Once **[use either "your health care provider" or the actual name of the entity, as above]** has disclosed your relative's protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your relative's confidentiality.

We may share your health information related to this study with other parties including U.S. and Canadian government regulatory and funding agencies, the **[insert local Institutional Review Boards]**, the coordinating centers at UTHealth and the Resuscitation Outcome Consortium (ROC) at the University of Washington. ROC is a clinical trial network which is providing additional study support for this research.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes **[use "your health care provider" or the actual name of the entity, as above]** to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by contacting **[PI name] at [telephone number, fax number and address.]** However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

The **[insert name of the entity holding the health records]** generally requires that we document in your medical record chart that you are taking part in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep the Informed Consent Document in our research files; and a copy **[will/will not, based on local policies]** be placed in your medical record chart.

NEW INFORMATION:

You will be told of any important new findings that may change your decision to continue in this study.

QUESTIONS:

Please feel free to ask any questions about this study or this consent form, either now or in the future. You can direct your questions to **[insert PI name]** at **[insert PI contact number]**. You have a right to ask questions and get satisfactory answers to all of your questions.

SIGNATURES:

[Insert language per local IRB policy/procedures]

Sign below if you understand the information given to you about the research and do not wish to withdraw yourself or your relative from this study.

_____

Subject or Legally Authorized Representative or Family Member (Printed Name)

_____ _____

Subject or Legally Authorized Representative or Family Member (Signature) Date and Time

_____

Person Obtaining Consent (Printed Name)

_____ _____

Person Obtaining Consent (Signature) Date and Time

Legally Authorized Representative/Subject Consent Form Template to Continue in the Study

INFORMED CONSENT TO CONTINUE A RESEARCH STUDY

Pragmatic, Randomized Optimal Platelet and Plasma Ratios
(PROPPR)

ENROLLMENT INTO THIS STUDY:

You were enrolled in this research study without giving informed consent because you required blood transfusions due to a life threatening injury. This research study is called, "Pragmatic, Randomized Optimal Platelet and Plasma Ratios," conducted by **[insert local PI name]** at **[insert local site name]**. For this research study **he/she** will be called the Principal Investigator or PI.

Your decision to stay in this study is voluntary and you may stop taking part in the study at any time. A decision to not take part in the research study will not change the services available to you from **[insert local PI name]** at **[insert local site name]**. This consent is to ask for your permission to CONTINUE with the tests and procedures with this study.

You may refuse to answer any questions asked or written on any forms.

If you were unable to provide written informed consent, a Legally Authorized Representative may have consented on your behalf to take part in this study.

DESCRIPTION OF RESEARCH:

PURPOSE:

The purpose of this study is to determine which combination of blood products given to trauma patients will improve survival. Blood contains many types of specialized cells flowing in liquid called plasma. *Red blood cells*, or RBCs, carry oxygen throughout the body. Cells called *platelets* have an important role in stopping bleeding after an injury. *Plasma* is mostly made up of water and it carries around the RBCs and platelets,

RBCs, plasma, and platelets are routinely given to patients who have experienced significant blood loss, but the best way to combine them for a patient who is bleeding is unknown. A "*unit*" refers to a bag of transfused RBCs, plasma, or platelets. The combination of blood products given to patients varies significantly. This research study will compare patient responses to 2 different combinations of RBCs, plasma, and platelets in common use

This study is being conducted in at least 12 different trauma centers in the US and Canada. A total of 680 subjects will participate across all sites. This location will enroll approximately **[insert #]** subjects. The National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), and Defence Research and Development Canada, are paying for this study to be completed.

PROCEDURES:

Since you were eligible to take part in this research study due to your severe bleeding, you have already received one of 2 potential combinations of RBCs, plasma, and platelets, and have had blood samples collected for study purposes. If you decide to stay in the research study, it will be necessary to collect more blood samples, and continue collecting information from the medical record. You can get out of the study at any time.

The research study involves the following sequence of events and procedures. A member of the research team will let you know what study procedures, if any, have already been done.

1. A trauma surgeon decided that blood transfusions were needed.
2. A member of the research team confirmed study eligibility, and randomly assigned (like the flip of a coin) you into 1 of 2 groups;
   - **One unit of red blood cells for every unit of platelets and plasma**
     - **OR**
   - **Two units of red blood cells for every unit of platelets and plasma**
3. Blood samples (about 2 tablespoons each), were collected at the time of arrival to the trauma center, and have been *or will be* collected at 2, 4, 6, 12, 24, 48, and at 72 hours after arrival (if still hospitalized).
   The blood samples drawn for this study will be used to look at 1) how your body has reacted to the injury, 2) how your blood is clotting (or clumping together) and 3) how your body has reacted to the fluids and treatments you received.

1. Information was and will be collected regarding the injury and the care received until you are discharged from the hospital or for the first 30 days of your hospital stay (whichever comes first). The information collected for this study will include lab values, surgery reports, vital signs (ex. blood pressure, heart and respiratory rate, and temperature) x-rays, and medicines you are taking. We collect this information to see how you are doing while you are in this study. We will check to see when you leave the hospital. If you leave **[name of hospital]** before day 30 after your injury we will, with your permission, call you to ask you how you are doing. If you were transferred to another hospital setting, we will ask for your permission to contact that facility to follow up on your progress. You will need to sign an additional HIPAA form to allow us permission to contact the other hospital and get your medical information. We will ask if you have experienced any problems since leaving the hospital. You have the right to refuse to answer any of the questions.

   You have received and will continue to receive all other standard of care treatments for your trauma injuries and were only enrolled in this protocol because it was predicted that you might require a massive transfusion. Although you were randomly assigned to receive one of two combinations of blood products, the amount of blood given to you was or will be based on your medical needs. Also, the blood transfusion was stopped based upon your medical needs.

BENEFITS:

You may receive no direct benefit from being in this study; however, your taking part may help severely injured patients get better care in the future.

RISKS AND/OR DISCOMFORTS:

The transfusion of any blood product carries a small risk of transmission of hepatitis, HIV (the virus that causes acquired immune deficiency syndrome, or AIDS), and other viral and infectious diseases, hypotension (low blood pressure), allergic reactions, shortness of breath, blood clotting complications, hypoventilation (too little air entering the lungs), and fever. Hospitals have established policies and procedures to safely transfuse blood products. You would have these risks whether or not you were in the study.

All the blood products used will be processed through **[site's blood bank name]**. All the blood products are approved by the U.S. Food and Drug Administration (FDA) and the American Association of Blood Banks (AABB) and/or Health Canada. All the blood given is typed and will be tested for infectious diseases. Hospitals have established policies and procedures to safely transfuse blood products. You would have these risks whether or not you were in the study but it is unknown at this time whether these risks are more severe or last longer (for example, lung injury) when one unit of red blood cells is administered for every unit of platelets and plasma compared with two units of red blood cells administered for every unit of platelets and plasma."

Possible risks with the blood collection include localized pain from the needle stick, swelling, and redness. Patients routinely have an intravenous (IV) catheter or tube inserted into a vein for the first few days after a major injury to provide fluids and medications. The research team will avoid additional needlesticks to patients whenever possible by collecting blood samples from existing IV catheters or during blood draws for other lab tests.

Another possible risk is a breach of confidentiality. Measures in place to protect confidentiality include the use of study numbers on blood samples and study records instead of patient names, and the use of password protected computers and encrypted databases. Electronic data will be stored on protected servers. Study records will be stored in locked file cabinets within locked offices.

ALTERNATIVES:

The alternative to continuing to be in this study is for you to receive the standard of careyou're your injury which includes the transfusion of blood products per local hospital policy.

STUDY WITHDRAWAL:

You can take yourself out of this study at any time without penalty and without affecting your future medical care at this center. If you choose to withdraw within the first 24 hours of treatment, you will be switched to routine blood transfusion therapy. The research team may also remove you from the study if they feel it is not in your best interest to continue taking part. If you decide to stop taking part in the study, no additional study procedures will be performed

and no further information will be collected. The information collected up to the time you chose to stop being in the study will remain in the research database and will be included in the data analysis.

IN CASE OF INJURY:

If you suffer any injury as a result of this study, please understand that nothing has been arranged to provide free treatment at **[insert site name]** or any other type of payment. However, all facilities, emergency treatment and professional services will be available to you use just as they are to the community in general. Please report any injury to **[insert PI name]** at **[insert PI contact number]** and **[if applicable, insert local IRB contact telephone number]**. You will not give up any of your legal rights by signing this consent form.

COST, COMPENSATION, and REIMBURSEMENT:

There are no additional costs for taking part in this study. You or your insurance will be responsible for all standard-of-care charges including the blood transfusions that are routinely given to trauma patients. You will not be charged for lab tests performed strictly for research purposes.

There will be no payment to you for taking part in this research study.

If you received a bill that you believe is related to your taking part in this research study, please contact **[insert PI name]** at **[insert PI contact number]** with questions.

CONFIDENTIALITY:

Please understand that representatives of the Food and Drug Administration (FDA), the **[insert local IRB name]**, the UTHouston Data Coordinating Center (HDCC), NHLBI, NIH, and Defence Research and Development Canada, may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. Your research records will be kept at **[insert local institution name]** for **[# years]** per **[name of institution]** policy.

There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information.

(OR use the wording below for sites which include the HIPAA language in this form)

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires **[use either "your health care provider" or the actual name of the entity holding the health records]** to obtain your permission for the research team to access or create protected health information about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health

condition or care. We will access or create health information about you relative, as described in this document, for purposes of this research study **[if applicable, add: and for your treatment]**. Once **[use either "your health care provider" or the actual name of the entity, as above]** has disclosed your relative's protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your relative's confidentiality.

We may share your health information related to this study with other parties including U.S. and Canadian government regulatory and funding agencies, the **[insert local Institutional Review Boards]**, the coordinating centers at UTHealth and the Resuscitation Outcome Consortium (ROC) at the University of Washington. ROC is a clinical trial network which is providing additional study support for this research.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes **[use "your health care provider" or the actual name of the entity, as above]** to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by contacting **[PI name] at [telephone number, fax number and address.]** However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

The **[insert name of the entity holding the health records]** generally requires that we document in your medical record chart that you are taking part in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep the Informed Consent Document in our research files; and a copy **[will/will not, based on local policies]** be placed in your medical record chart.

NEW INFORMATION:

You will be told of any important new findings that may change your decision to continue in this study.

QUESTIONS:

Please feel free to ask any questions about this study or this consent form, either now or in the future. You can direct your questions to **[insert PI name]** at **[insert PI contact number]**. You have a right to ask questions and get satisfactory answers to all of your questions.

SIGNATURES:

[Insert language per local IRB policy/procedures]

Sign below if you understand the information given to you about the research and do not wish to withdraw your relative from this study.

_____

Subject or Legally Authorized Representative or Family Member (Printed Name)

_____ _____

Subject or Legally Authorized Representative or Family Member (Signature) Date and Time

_____

Person Obtaining Consent (Printed Name)

_____ _____

Person Obtaining Consent (Signature) Date and Time

Child Assent Form Template

RESEARCH STUDY INFORMATION AND ASSENT FORM FOR MINORS
(For use when the LAR/family member has already signed a consent form)

Title: Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)

(Participating Site IRB#_____)

You were enrolled in a research study while you were in the emergency department receiving care. We did this by using a process regulated by federal and state laws, called an emergency research consent waiver. The emergency consent waiver allows researchers to enroll patients with life-threatening medical conditions who cannot give informed consent where study treatments have to be started before informed consent from the subject's legally authorized representative or family member can be obtained. Your parent, family member, or legally authorized representative have already received or will also be given a consent form to review. That consent form describes the study, (purpose, procedures, risks, benefits) in detail.

PURPOSE:
The purpose of this study is to determine which combination of blood products given to trauma patients will improve survival. Blood contains many types of specialized cells flowing in liquid called plasma. *Red blood cells*, or RBCs, carry oxygen throughout the body. Cells called *platelets* have an important role in stopping bleeding after an injury. *Plasma* is mostly made up of water and it carries around the RBCs and platelets,
RBCs, plasma, and platelets are routinely given to patients who have experienced significant blood loss, but the best way to combine them for a patient who is bleeding is unknown. A "*unit*" refers to a bag of transfused RBCs, plasma, or platelets. The combination of blood products given to patients varies significantly. This research study will compare patient responses to 2 different combinations of RBCs, plasma, and platelets in common use

This study is being conducted in at least 12 different trauma centers in the US and Canada. A total of 680 subjects will participate across all sites. This location will enroll approximately **[insert #]** subjects. The National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), and Defense Research and Development Canada, are paying for this study to be completed.

PROCEDURES:
Since you were eligible to take part in this research study due to your severe bleeding, you have already received one of 2 potential combinations of RBCs, plasma, and platelets, and have had blood samples collected for study purposes. If you decide to stay in the research study, it will be necessary to collect more blood samples, and continue collecting information from the medical record. You can get out of the study at any time.
The research study involves the following sequence of events and procedures. A member of the research team will let you know what study procedures, if any, have already been done.

1. A trauma surgeon decided that blood transfusions were needed.
2. A member of the research team confirmed study eligibility, and randomly assigned (like the flip of a coin) you into 1 of 2 groups;

- **One unit of red blood cells for every unit of platelets and plasma**
  - **OR**
- **Two units of red blood cells for every unit of platelets and plasma**

3. Blood samples (about 2 tablespoons each), were collected at the time of arrival to the trauma center, and have been *or will be* collected at 2, 4, 6, 12, 24, 48, and at 72 hours after arrival (if still hospitalized).
   The blood samples drawn for this study will be used to look at 1) how your body has reacted to the injury, 2) how your blood is clotting (or clumping together) and 3) how your body has reacted to the fluids and treatments you received.
4. Information was and will be collected regarding the injury and the care received until you are discharged from the hospital or for the first 30 days of your hospital stay (whichever comes first). The information collected for this study will include lab values, surgery reports, vital signs (ex. blood pressure, heart and respiratory rate, and temperature) x-rays, and medicines you are taking. We collect this information to see how you are doing while you are in this study. We will check to see when you leave the hospital. If you leave **[name of hospital]** before day 30 after your injury we will, with your permission, call you to ask you how you are doing. If you were transferred to another hospital setting, we will ask for your permission to contact that facility to follow up on your progress. You will need to sign an additional HIPAA form to allow us permission to contact the other hospital and get your medical information. We will ask if you have experienced any problems since leaving the hospital. You have the right to refuse to answer any of the questions.

You have received and will continue to receive all other standard of care treatments for your trauma injuries and were only enrolled in this protocol because it was predicted that you might require a massive transfusion. Although you were randomly assigned to receive one of two combinations of blood products, the amount of blood given to you was or will be based on your medical needs. Also, the blood transfusion was stopped based upon your medical needs.

BENEFITS:

You may receive no direct benefit from being in this study; however, your taking part may help severely injured patients get better care in the future.

RISKS AND/OR DISCOMFORTS

The transfusion of any blood product carries a small risk of transmission of hepatitis, HIV (the virus that causes acquired immune deficiency syndrome, or AIDS), and other viral and infectious diseases, hypotension (low blood pressure), allergic reactions, shortness of breath, blood clotting complications, hypoventilation (too little air entering the lungs) and fever. Hospitals have established policies and procedures to safely transfuse blood products. You will have these risks, because of the blood transfusion you will receive to treat your injury, whether or not you are in the study.

All the blood products used will be processed through **[site's blood bank name]**. All the blood products are approved by the U.S. Food and Drug Administration (FDA) and the American Association of Blood Banks (AABB) and/or Health Canada. All the blood given is typed and will be tested for infectious diseases. Hospitals have established policies and procedures to safely transfuse blood products. You would have these risks whether or not you were in the study but it is unknown at this time whether these risks are more severe or last longer (for

example, lung injury) when one unit of red blood cells is administered for every unit of platelets and plasma compared with two units of red blood cells administered for every unit of platelets and plasma."

Possible risks with the blood collection include localized pain from the needle stick, swelling, and redness. Patients routinely have an intravenous (IV) catheter or tube inserted into a vein for the first few days after a major injury to provide fluids and medications. The research team will avoid additional needlesticks to patients whenever possible by collecting blood samples from existing IV catheters or during blood draws for other lab tests.

Another possible risk is a breach of confidentiality. Measures in place to protect confidentiality include the use of study numbers on blood samples and study records instead of patient names, and the use of password protected computers and encrypted databases. Electronic data will be stored on protected servers. Study records will be stored in locked file cabinets within locked offices.

ALTERNATIVES:

The alternative to continuing to be in this study is for you to receive the standard of care you're your injury which includes the transfusion of blood products per local hospital policy.

STUDY WITHDRAWAL:

You may choose to stop being a part of this study at any time. If you choose to stop taking part in this study, no additional information will be collected. The information collected up to the time you chose to stop being in the study will remain in the research database and will be included in the data analysis. The information we collect for the study is coded to protect privacy. You will not be personally identified in any reports.

If you agree to remain in the study, you will not be asked to return for any visits after hospital discharge.

QUESTIONS:

Please feel free to ask any questions about this study or the consent form. If you choose to continue in this study, please check next to the Yes and sign below. If you choose to stop taking part in this study, please check next to the No and sign below. You will be provided with a copy of this signed assent form.

_____ Yes, I want to continue being a part of this study.

_____ No, I want to stop being a part of this study.

Subject Name (printed): _____

Subject's Signature _____ Date _____

Name of person obtaining consent _____

Signature of person obtaining consent _____Date _____

Informed Consent for Blood Sample Collection Template

INFORMED CONSENT FOR BLOOD SAMPLE COLLECTION
Pragmatic, Randomized Optimal Platelet and Plasma Ratios
(PROPPR)

ENROLLMENT INTO THIS STUDY

You were enrolled in this research study without giving informed consent because you are __ years or older, have experience physical trauma, and needed immediate care in the emergency department. This research study is called Pragmatic, randomized Optimal Platelet and Plasma Ratios, conducted by [insert local PI name] at [insert local site name]. For this research project, he/she will be called the Principal Investigator or PI.

Your decision to take part is voluntary and you may refuse to take part, or choose to stop from taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from [insert local PI name] at [insert local site name].

You may refuse to answer any questions asked or written on any forms.

If you were unable to provide written informed consent, a Legally Authorized Representative (LAR) may have consented on your behalf to take part in this study.

DESCRIPTION *OF RESEARCH*:

PURPOSE:

The purpose of this study is to look at how your body reacts (on a cellular level) to the injuries you have as a result of the trauma event. Blood samples (about 2 tablespoons or 23 cc.) were collected at the time of arrival to the emergency department (ED). The blood samples that were drawn will be used to look at 1) how your body has reacted to the injury, 2) how your blood is clotting (or clumping together) and 3) how your body has reacted to the fluids and treatments you received. These samples will not be used for any genetic testing.

PROCEDURE:

You were eligible to take part in this study but were unable to give informed consent because of your potentially life-threatening injury. When you arrived to the Emergency Department (ED), blood samples were drawn for research purposes. These samples are not used for clinical care and not needed for the physicians to make decisions on your care. The purpose of this study is to look at the results from these samples.

Information was and/or will be collected regarding the injury and the care you received until you were discharged from the hospital. The information collected will include demographics (race,

age, sex), details of injury (type of injury, type of accident, time, number of injuries), lab values, vital signs (blood pressure, heart rate, temperature, and respirations), surgery reports and any x-rays and medicine you are taking. You have the right to refuse for us to look at your information.

The blood samples that were drawn when you arrived to the ED will be processed and stored for future trauma research studies with your permission. If you decide to continue to take part in this study, you will be asked how you would like your samples to be used. Please pick one of the choices below:

____ My blood and other information may be kept and used in research to learn about and treat trauma injuries.

____ My blood and other information may be kept and used in research to learn about and treat trauma injuries or other health problems.

____ My blood and other information may not be used in future studies.

TIME COMMITMENT*:*

If you agree to take part in this study, you will not be asked to come back for any visits after hospital discharge. We will not be asking for any extra blood to be drawn for study purposes.

BENEFITS:

You will receive no direct benefit or payment from taking part in this study; however, your taking part may help patients get better care in the future.

RISKS AND/OR DISCOMFORTS*:*

A possible risk associated with this study is a breach of confidentiality. All information collected for the purposes of this study will be de-identified. You will be identified by a study number. The blood samples will be labeled with the study ID number. The information used from your medical record will be coded with the study ID number. The paper records will be in locked cabinets in a locked office and the electronic records will be maintained in a password protected computer.

You will not be contacted in regard to any results or information which is obtained from these samples.

ALTERNATIVES*:*

The only alternative is not to take part in this study.

STUDY *WITHDRAWAL*:

You can take yourself out of this study at any time without penalty and without affecting your future care at this center. If you agree to have your samples stored for future use, you can change your mind. You have the right to have your sample destroyed. Any analysis that was done before the request cannot be removed; however no further testing will be done and all remaining samples will be destroyed. This means that if you decide to withdraw from this research study, the data collected prior to withdrawal may still be used up to the point of withdrawal. You may withdraw from any future analysis of the information or samples collected for this study in writing or by calling (xxx) xxx-xxxx.

IN CASE OF INJURY*:*

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to [insert PI name] at [insert PI contact number] and [if applicable, insert local IRB name and contact telephone number] . You will not give up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT, AND COMPENSATION*:*

There are no additional costs for taking part in this study. You or your 3rd party payer will be responsible for all standard-of-care charges during your hospital stay. You will not be charged for the lab tests done specifically for this research study.

There will be no payment to you for taking part in this research study.

If you received a bill that you believe is related to your taking part in this research study, please contact [insert PI name] at [insert PI contact number] with questions.

CONFIDENTIALITY:

Please understand that representatives of the Food and Drug Administration (FDA), the **[insert local IRB name],** the UTHouston Data Coordinating Center (HDCC), NHLBI, NIH, and Defence Research and Development Canada, may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. Your research records will be kept at **[insert local institution name]** for **[# years]** per **[name of institution]** policy.

There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information.

(OR use the wording below for sites which include the HIPAA language in this form)

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires **[use either "your health care provider" or the actual name of the entity holding the health records]** to obtain your permission for the research team to access or create protected health information about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you relative, as described in this document, for purposes of this research study **[if applicable, add: and for your treatment]**. Once **[use either "your health care provider" or the actual name of the entity, as above]** has disclosed your relative's protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your relative's confidentiality.

We may share your health information related to this study with other parties including U.S. and Canadian government regulatory and funding agencies, the **[insert local Institutional Review Boards]**, the coordinating centers at UTHealth and the Resuscitation Outcome Consortium (ROC) at the University of Washington. ROC is a clinical trial network which is providing additional study support for this research.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes **[use "your health care provider" or the actual name of the entity, as above]** to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by contacting **[PI name] at [telephone number, fax number and address.]** However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

The **[insert name of the entity holding the health records]** generally requires that we document in your medical record chart that you are taking part in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep the Informed Consent

Document in our research files; and a copy **[will/will not, based on local policies]** be placed in your medical record chart.

QUESTIONS:

Please feel free to ask any questions about the study or this consent form, either now or in the future. You can direct your questions to [insert PI name] at [insert PI contact number]. You have a right to ask questions and get satisfactory answers to all of your questions.

NEW INFORMATION:

You will be told of any important new findings that may change your decision to continue in this study.

SIGNATURES:

[Insert language per local IRB policy/procedures.]

Sign below only if you understand the information given to you about the research and choose to take part.

_____
Subject (Printed Name)

_____ _____
Subject (Signature) Date and Time of Signature

_____
Legally Authorized Representative or Family Member (Printed Name)

_____ _____
Legally Authorized Representative or Family Member (Signature) Date and Time of Signature

_____
Person Obtaining Consent (Printed Name)

_____ _____
Person Obtaining Consent (Signature) Date and Time of Signature

Section 2.4 PROPPR Consent Procedures

Obtaining Informed Consent

The following guidelines should be followed for obtaining a written informed consent following the patient's hospital admission:

- Once the subject is randomized, the PI and/or a designated member of the clinical research team (listed in block 6 of the site's 1572) **must** make frequent attempts as soon as feasible (please follow your local IRB requirements for the frequency of the attempts).
- Follow your local IRB requirements regarding the methods of obtaining consent (i.e. direct contact, telephone contact, written contact or any other contact as long as it is approved by your IRB).
- For those subjects considered as a minor, follow your local IRB regulations for acquiring the assent (note: If your local IRB does not require an assent form signed, please document accordingly).
- The LAR is the legally authorized representative – please verify who is considered a LAR with your state regulations.
- Follow your local IRB requirements regarding written notification to the family in the event the subject expired prior to obtaining study consent.
- In the event the subject is unable to provide the initial consent (LAR signed the consent form), remember to speak with the subject (when they are alert and able to provide consent) to obtain their consent for the study in addition to the LAR's consent.
- Follow your local IRB guidelines regarding use of data collected up to time of LAR and/or subject's withdrawal of continuing in the study.
- See Section 2.4.2 for Subject/LAR consent log and instructions
- In the event that the subject does not survive, their information will be included in the data analysis, thus written notification may be sent to the deceased's family regarding their participation in the study, per local IRB/REB policy (See Section 2.4.3)
- Further information on the consent process is located in Section 12 and Appendix 1 of the PROPPR protocol.

Time Frame for Obtaining Consent

- In the event your local IRB does not mandate specific time intervals, it is recommended that the research team attempt to contact the patient and/or LAR at a minimum of every 4 hours during the first 24 hours and a minimum of daily thereafter.
- Multiple attempts should be made to obtain consent prior to the last research sample is collected (72 hours after ED admission).
- In the event, contact has not been made prior to the 72 hour window, please continue to make frequent attempts to contact the patient/LAR throughout the hospitalization.
- A log (Section 2.4.1) is included in the data collection form for documentation of all attempts to reach patient/LAR.

Section 2.4.1 General Instructions for Completing CRF Form # 19.

This form is optional for screening failures and required for all randomized subjects. Use this from to record contacts with the subject or LAR. Source documents include the hospital record, direct data entry into the CRF. Print additional pages if needed.

Record all dates and times in dd/mmm/yy and hh:mm formats.

Indicate the purpose of the contact, how contact was attempted, and the outcome or results of the contact.

CRF Form 19: Subject / LAR Contact Log

(Document attempts to contact LAR for consent OR Subject/LAR for 30 day follow-up status here.)

Check here ☐ if subject died before contact with LAR could be attempted.

Date	Time *(hh:mm)*	Purpose	Type of Contact	Result
/ /	:	☐ Contacting LAR for Consent ☐ Contacting Subject/ LAR for 30 Day Status	☐ Phone ☐ Clinic Visit ☐ Letter/Certified Letter ☐ In Person ☐ e-mail ☐ Other: ____________	☐ Made Contact, Consent Given ☐ Made Contact, Consent Not Given ☐ No Reply, Did Not Make Contact ☐ Note Additional Information on Form #22
/ /	:	☐ Contacting LAR for Consent ☐ Contacting Subject/ LAR for 30 Day Status	☐ Phone ☐ Clinic Visit ☐ Letter/Certified Letter ☐ In Person ☐ e-mail ☐ Other: ____________	☐ Made Contact, Consent Given ☐ Made Contact, Consent Not Given ☐ No Reply, Did Not Make Contact ☐ Note Additional Information on Form #22
/ /	:	☐ Contacting LAR for Consent ☐ Contacting Subject/ LAR for 30 Day Status	☐ Phone ☐ Clinic Visit ☐ Letter/Certified Letter ☐ In Person ☐ e-mail ☐ Other: ____________	☐ Made Contact, Consent Given ☐ Made Contact, Consent Not Given ☐ No Reply, Did Not Make Contact ☐ Note Additional Information on Form #22
/ /	:	☐ Contacting LAR for Consent ☐ Contacting Subject/ LAR for 30 Day Status	☐ Phone ☐ Clinic Visit ☐ Letter/Certified Letter ☐ In Person ☐ e-mail ☐ Other: ____________	☐ Made Contact, Consent Given ☐ Made Contact, Consent Not Given ☐ No Reply, Did Not Make Contact ☐ Note Additional Information on Form #22
/ /	:	☐ Contacting LAR for Consent ☐ Contacting Subject/ LAR for 30 Day Status	☐ Phone ☐ Clinic Visit ☐ Letter/Certified Letter ☐ In Person ☐ e-mail ☐ Other: ____________	☐ Made Contact, Consent Given ☐ Made Contact, Consent Not Given ☐ No Reply, Did Not Make Contact ☐ Note Additional Information on Form #22
/ /	:	☐ Contacting LAR for Consent ☐ Contacting Subject/ LAR for 30 Day Status	☐ Phone ☐ Clinic Visit ☐ Letter/Certified Letter ☐ In Person ☐ e-mail ☐ Other: ____________	☐ Made Contact, Consent Given ☐ Made Contact, Consent Not Given ☐ No Reply, Did Not Make Contact ☐ Note Additional Information on Form #22

(Print additional pages if needed)

Section 2.4.2 General Instructions for Completing CRF Form # 20

Complete this form for all randomized subjects. Use this form to record subject or LAR consent. Source documents include the hospital record, direct data entry into the CRF.

Question #1:	Indicate if the LAR was notified of the subjects' participation in the study. If "yes" is selected, indicate the relationship to the subject and record the date and time of the notification using dd/mmm/yy and hh:mm formats.
Question #2:	Indicate if consent was obtained for study participation. If "yes" is selected, indicate the relationship to the subject and record the date and time using dd/mmm/yy and hh:mm formats.
Question #3:	Indicate if consent was obtained for a follow-up call for the Day 30 vital status information. If "yes" is selected, indicate the relationship to the subject and record the date and time using dd/mmm/yy and hh:mm formats.
Question #4:	Indicate if HIPAA consent was obtained to contact another facility for the Day 30 vital status information. If "yes" is selected, indicate the relationship to the subject and record the date and time using dd/mmm/yy and hh:mm formats.

CRF Form # 20 Subject/LAR Consent Log

Check here ☐ if subject died before contact with LAR could be attempted.

1. Was the subjects' LAR notified of their participation?

□ Yes (Check all that apply)
□ Subject Date: ___/____/___ Time: ___ : ___
□ LAR Date: ___/____/___ Time: ___ : ___
□ No

2. Was consent obtained for study participation?

□ Yes (Check all that apply)
□ Subject Date: ___/____/___ Time: ___ : ___
□ LAR Date: ___/____/___ Time: ___ : ___
□ No

3. Was consent obtained for a follow-up call for Day-30 status?

□ Yes (Check all that apply)
□ Subject Date: ___/____/___ Time: ___ : ___
□ LAR Date: ___/____/___ Time: ___ : ___
□ No
□ Not Applicable

4. Was HIPAA consent obtained to collect Day-30 status (if discharged to another care facility)?

□ Yes (Check all that apply)
□ Subject Date: ___/____/___ Time: ___ : ___
□ LAR Date: ___/____/___ Time: ___ : ___
□ No
□ Not Applicable

Section 2.4.3 Deceased Subject Letter Template

Letter to the Family of Deceased Subject Template

[Site Letterhead]

Date
To the Family of ***[Patient's Name]***
Address

Dear Family Member:

We understand this letter may come at a time that is difficult for your family and we offer our sincere condolences for your recent loss. We are aware a death after trauma is an unexpected event and may have difficult personal consequences.

Our [Institution/Hospital] emergency department service records show that [Patient's Name] was treated for blood loss related to a traumatic injury or injuries. When your relative was being treated in our emergency department, he/she was likely unconscious and unable to reliably talk with us about his/her wishes. While your relative was undergoing immediate treatment and resuscitative interventions, it was determined that [patient name] would need to receive approved blood products as part of the usual care for trauma patients with severe bleeding. During this time, your relative was enrolled in an approved clinical research study called the "Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Study." Based on the randomization plan (a process like flipping a coin), [patient name] received one of 2 combinations of RBCs, plasma, and platelets which are all commonly used at [name of institution], and had blood samples collected for study purposes. In addition, routine clinical information from [patient's name] record was recorded as part of the study. We are writing to inform you that this has occurred; no further action on your part is required. Your family member's personal information will remain confidential.

Your family member's participation in this study will help us to better understand trauma patients who experience severe bleeding and how we can improve the care of future trauma patients. Our study evaluates the usual care and procedures routinely performed in emergency centers throughout the United States and Canada. If you would like to know more about the study, please contact [name and phone number of the local primary investigator].

The ***[Institution/Hospital]*** Ethics Board/Institutional Review Board has given us permission to do this study in which subjects are enrolled without their individual consent. This process is called exception from informed consent for emergency research ***[or ' waiver of consent' for Canadian sites]***. The study is overseen by a Data Safety and Monitoring Committee, which is an independent committee that periodically reviews information from the study to ensure patient safety.

The study is being done throughout the United States and Canada by a network called the Resuscitation Outcomes Consortium (ROC), of which I am a member. This study is funded by grants received from the U.S. National Institutes of Health and the Canadian Institutes of Health Research.

You have the right to have your family member's sample destroyed. Any analysis that was done before the request cannot be removed; however no further testing will be done and all remaining samples will be destroyed. This means that if you decide to withdraw your family member from this research study, the data collected prior to withdrawal may still be used up to the point of withdrawal. You may withdraw your family member from any future analysis of the information or samples we collected for this study by calling *(xxx) xxx-xxxx.*

If you would like to discuss any of this further, please contact me, Dr. ***[PI name],*** the doctor responsible for the study, or ***[Primary Research Study Coordinator]*** at ***[phone number].*** Also, you can contact the ***[Institution/Hospital]***'s Ethics Board/Institutional Review Board at ***[phone number]***

We apologize for this intrusion. We do appreciate how difficult this situation may be for you and your family.

Kind regards,

[PI Name, M.D.
Title/Institution]

Section 2.5 Blood Sample Consent from Screening Failures

A modified consent process will be conducted in the group of subjects who are screened, have initial blood drawn, and determined to be eligible (at the 0 hour blood draw) but are not randomized. The method of consent (i.e. waiver of consent, waiver of documentation, or full consent) will be dependent on the individual site's local IRB/REB policies and regulations. Refer to Section 2.3.1 for a sample consent for use of the research blood sample.

Section 2.5.1 General Instructions for Completing CRF Form # 24

Complete this form only for screening failures.

Question #1: Select the Site IRB approved method for consent to use the first available research blood sample, or IRB waiver of consent, if applicable. If “waiver of consent” is selected, stop here.

Question #2: Document contact attempts to obtain consent. Record the date and times using dd/mmm/yy and hh:mm formats. Indicate who was contacted, the contact method used, and the results of the contact.

Question #3: Indicate if consent was obtained. If “yes” is selected, continue to the next question. If “no” is selected, skip question #4 and proceed to question #5.

Question #4: Indicate if any restriction were places on the use of the research blood sample.

Question #5: If IRB consent for the research blood sample was required but never obtained, indicate if the sample was destroyed?

CRF Form # 24 Blood Sample Consent/Contact Record for Screening Failures

1. What IRB approved method was used to obtain consent for use of the first available research blood sample? *(Select one)*
   - □ Modified Informed consent for 1 research blood sample and registry data collection. *(Continue to next question)*
   - □ Not applicable, local site IRB waiver of informed consent. *(Stop here)*

2. Document contact attempts below. **Check here** □ if the patient died before contact with LAR could be attempted.

Date *(dd/mmm/yy)*	**Time** *(24hr Clock in hh:mm)*	**Contact Source**	**Type of Contact**	**Result**
/ /	:	□ Patient □ LAR	□ Phone □ Clinic Visit □ Letter/Certified Letter □ In Person □ e-mail □ Other: ___________	□ Made Contact □ No Reply, Did Not Make Contact □ Note Additional Information on Form #22
/ /	:	□ Patient □ LAR	□ Phone □ Clinic Visit □ Letter/Certified Letter □ In Person □ e-mail □ Other: ___________	□ Made Contact □ No Reply, Did Not Make Contact □ Note Additional Information on Form #22
/ /	:	□ Patient □ LAR	□ Phone □ Clinic Visit □ Letter/Certified Letter □ In Person □ e-mail □ Other: ___________	□ Made Contact □ No Reply, Did Not Make Contact □ Note Additional Information on Form #22
/ /	:	□ Patient □ LAR	□ Phone □ Clinic Visit □ Letter/Certified Letter □ In Person □ e-mail □ Other: ___________	□ Made Contact □ No Reply, Did Not Make Contact □ Note Additional Information on Form #22
/ /	:	□ Patient □ LAR	□ Phone □ Clinic Visit □ Letter/Certified Letter □ In Person □ e-mail □ Other: ___________	□ Made Contact □ No Reply, Did Not Make Contact □ Note Additional Information on Form #22
/ /	:	□ Patient □ LAR	□ Phone □ Clinic Visit □ Letter/Certified Letter □ In Person □ e-mail □ Other: ___________	□ Made Contact □ No Reply, Did Not Make Contact □ Note Additional Information on Form #22

3. Was informed consent obtained?
   - □ Yes *(Continue to next question)* □ No *(Go to question #5)*

4. What option below did the Patient/LAR Select for use of the blood sample? *(Select one)*
   - □ Blood sample and other information may be kept and used in research to learn about and treat trauma injuries.
   - □ Blood sample and other information may be kept and used in research to learn about and treat trauma injuries or other health problems.
   - □ Blood sample and other information may not be used in future studies.
   - □ No restrictions on use of the blood sample were given.

5. If consent for the first available lab sample was NOT obtained, was the lab sampled destroyed?
   - □ Yes □ No

Section 2.6 General Instructions for Completing CRF Form # 21

Complete this form for all randomized subjects. Indicate if any of the criteria were met during the study. Source documents include the hospital medical record or direct data entry into the CRF.

Record all dates and times in dd/mmm/yy and hh:mm formats.

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___ **(Bar Code)**

CONFIDENTIAL

CRF Version Date: 2013 MAR 01 Completed By: ___ ___ ___

Form 21: End of Study *(Complete this form for all randomized subjects.)*

Were any of the following criteria met?	**Yes**	**No**	**Date** *(dd/mmm/yy)*	**Time** *(24hr Clock in hh:mm)*
The subject withdrew consent.	☐	☐	/ /	:
The subjects' legally authorized representative withdrew consent.	☐	☐	/ /	:
The subject was detained or incarcerated before the study was completed.	☐	☐	/ /	:

Chapter 3 – Screening

Section 3.1 Overview

Subjects meeting the sites highest level of trauma activation will be screened for eligibility to participate in the clinical trial and assigned a study ID with the first two digits indicating the clinical site, and the remaining 5 digits sequential numbers in the order screened. Data will be collected prospectively during the trial beginning at ED arrival and will continue until 1) it has been determined that the subject is not eligible for this trial, 2) the subject or LAR refuses continuation in the trial, 3) the subject has achieved hemostasis, 4) the subject has expired or 5) 24 hours have elapsed, whichever comes first. Until deemed ineligible, data from subjects will be collected and reviewed for screening purposes. Data on in-eligibility will be submitted to the HDCC to allow a description of screened versus enrolled subjects. For randomized subjects, data will be collected from a review of the medical records and results of diagnostic studies from admission until discharge or day 30 of the initial hospitalization.

Section 3.2 Screening

Clinical research staff will be available in the hospital at each center on a 24/7 basis to conduct screening for PROPPR. The research staff will screen all major trauma subjects admitted to the ED with the highest acuity status*. Data collection, blood draw for time 0**, and subject observation will begin on the highest acuity subjects immediately upon the patient's arrival to the ED.

*For further clarification, the research staff should follow the process utilized by the clinical trauma team for responding to the highest acuity trauma activation *(i.e. If the trauma attending responds, the PROPPR research team should also respond).*

If there is an **initial obvious exclusion *(i.e. prisoner, 10 year old, etc.)* the 0 hour sample should not be drawn. However, CRF forms #1 and #2, should be completed.

Once it is determined that the subject is ineligible, data collection will cease.

For subjects meeting the PROPPR eligibility criteria, the research staff will perform an assessment using the validated ABC score. Subjects with two or more positive variables from the ABC score on admission will be eligible to be randomized in the trial and receive the PROPPR transfusion protocol. The clinical person responsible for implementing physician orders will notify the blood bank per standard procedure at each institution.

In subjects with fewer than two of these variables, the PROPPR research staff will query the trauma attending as to their clinical judgment regarding whether the patient will require a MT. If the attending responds with a "yes" the patient will be eligible for the trial. The physician can wait to respond to the gestalt question, if unsure; however, he or she must respond within one hour of ED admission to activate the protocol. If the answer, however, is "no" the patient will be considered ineligible and all study procedures will end. The data collected up to the time the patient is deemed ineligible will be kept at each site and submitted to the HDCC to allow a description of screened patients versus enrolled subjects and provide demographic data for the blood samples analyses.

The HCCC/HDCC will only receive de-identified research records/data. The clinical data required to calculate the ABC score is routinely acquired at Level I trauma centers and should be available within minutes of arrival on all potential subjects.

See Chapter 18 for information on the 1st available research lab sample.

Section 3.2.1 General Instructions for Completing Screening CRF Form #1

Complete this form for all potential subjects requiring your sites highest level of trauma activation. Stop data collection at the point the patient is determined ineligible to participate in the study. Questions # 1, 6 and 11 should be completed for all screened patients.

Based on EMS/Trauma alert information and site specific policies, pre-order randomized PROPPR blood products if indicated.

Question #1: Complete this question for all screened subjects. Enter the emergency department (ED) arrival date and time. The ED arrival time represents "Time Zero" for protocol procedures and later interventions. Source Documents: Hospital ED record or direct observation and data entry into the CRF.

Question #2: Enter the first available vital signs and Glasgow Coma Score (GCS) after arrival in the ED. Select the unit of measure for temperature. Use the following key for GCS scoring. Record the total GCS if component scores are unavailable.

GCS Scoring Key

Eye Movement (E)		Verbal (V)		Motor (M)	
1	No Response	1	No Response / Intubated	1	No Response
2	To Pain	2	Incomprehensible Sounds	2	Extension *(Decerebrate)*
3	To Verbal Command	3	Inappropriate Words	3	Flexion – *(Decorticate)*
4	Spontaneous	4	Disoriented, Converses	4	Flexion – Withdrawals From Pain
		5	Oriented, Converses	5	Localizes Pain
				6	Obeys Commands Appropriately

Indicate whether or not the patient had an advanced airway at the time the verbal GCS component was assessed. For the purpose of GCS, the verbal score should be "1" in the presence of an advanced airway. Advanced airway is defined here as a device used as a method to assist and/or control ventilation. These devices mechanically prohibit verbal response testing. Devices used to assist and/or control ventilation are: bag value mask, oral ET, nasal ET, Combitube, LMA, King airway, and cricothyrotomy/tracheostomy.

Indicate if the patient was chemically paralyzed at the time of the assessment. Paralytic drugs are defined as Pancuronium Bromide, Rocuronium, Succinylcholine, or Vercuronium.

Source Documents: Hospital ED record or direct observation and data entry into the CRF.

Question #3: Calculate the assessment of blood consumption (ABC) score by answering yes or no to the 4 questions listed. For each question, a yes response equals 1 point and a no response zero. Note: Question 3 (a) is defined as penetrating mechanism of injury. Calculate the total ABC score. Source Document: Hospital Lab results and direct observation and data entry into the CRF.

Question #4: Indicate if the ABC score was 2 or greater. If the total ABC score is 2 or greater, *(following institutional policies and procedures)* notify blood bank of PROPPR MT protocol subject and request randomized blood products. Proceed to question #6. If the total ABC score is less than 2, proceed to next question.

The research TEG/Multiplate sample should be processed for subjects with an ABC score of 2 or greater. HOLD the TEG/Multiplate sample if the ABC score is less than 2 pending the Trauma Attending response to question #5.

Source Document: Direct observation and data entry into the CRF.

Question #5: Ask the Trauma Attending if a MT is needed and the time answered. This question should be asked immediately after calculating the ABC score and cannot be repeated. The Trauma Attending may delay responding and indicate he/she is still assessing the patient. Randomized blood products must be ordered within 1 hour of ED arrival.

If the Trauma Attending indicates "yes", *(following institutional policies and procedures)* notify the blood bank of PROPPR MT protocol subject and request randomized blood products.

If the Trauma Attending indicates "no", the patient will be considered a screening failure. Complete the remaining questions on form #1 as applicable.

Follow site policy on TEG/Multiplate research sample processing for screening failures.

Source Document: Direct observation and data entry into the CRF.

Question #6: Answer this question for all screened subjects. Indicate if a research blood sample was collected. If "no", document the reason on form #22 and proceed to the next form. If "yes", record the blood sample collection time and collection tube information as listed. The collection tubes should be filled in the following order: 2.7 ml blue top R1 (Teg/Multiplate), one 4.5ml blue top R2, one 4.5ml R4 citrate tube, the second 4.5ml blue top R3, and the lavender core lab flow tube last R5. Indicate if problems occurred during research blood sample collection. If "yes", indicate the appropriate problem code from the list provided or select "other" and document on form #22. Blood sample collection problems are defined as (a.) excessive bleeding after venipuncture, (b.) loss of vacuum during collection, (c.) hematoma, (d.) Other. Attach a lab ID barcode label in the space provided using ***either*** a label for screening failure or a randomized subject.

6. First Available Blood Sample: **Check here** ☐ if the blood sample was not collected & proceed to next form. Document the reason for not collecting the sample on form # 22.

Blood Draw Time (hh:mm)	COAGs. (Blue Top Sodium Citrate)			R4 Blue 4.5 mL Citrate/Benzamidine	R5 Lavender 5 mL (FLOW for CORE Lab)
	R1 Blue 2.7 mL Tube (Site TEG/Multiplate)	R2 Blue 4. 5 mL Tube	R3 Blue 4.5 mL Tube		
:	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube
**Indicate if any problems occurred during collection	☐ Yes (check reason code) ☐ a ☐ b ☐ c ☐ d ☐ No	☐ Yes (check reason code) ☐ a ☐ b ☐ c ☐ d ☐ No	☐ Yes (check reason code) ☐ a ☐ b ☐ c ☐ d ☐ No	☐ Yes (check reason code) ☐ a ☐ b ☐ c ☐ d ☐ No	☐ Yes (check reason code) ☐ a ☐ b ☐ c ☐ d ☐ No
Attach CRF Lab ID Label Here →			LabID: 10001 CRF Label		

Source Document: Direct observation and data entry into the CRF.

Question #7: Indicate if TEG/Multiplate lab values will be reported.

Question #8 Indicate the anatomical site used for the research blood sample collection.
Source Document: If "other" is selected, record the anatomical site in the space provided. Direct observation and data entry into the CRF.

Question #9: Indicate the technique used to obtain the research blood sample.
Source Document: Direct observation and data entry into the CRF.

Question #10: Estimate the amount of blood and IV fluids given from pre-hospital to the 1st available research blood sample collection.

Source Document: Direct observation and data entry into the CRF.

Crystalloids vs. Colloids

Crystalloids are fluids that contain a combination of water and electrolytes. Common examples are NS, LR, D5W, D51/2 NS, D5 ¼, NS and Plasmalyte. Crystalloid solutions closely mimic the body's extra cellular fluid. Given I.V., crystalloid solutions diffuse through the capillary walls that separate plasma from interstitial fluid. They can be used to expand both intravascular and extra vascular fluid volume.

Colloids are fluids that contain dissolved particles, such as protein, sugar, and starch molecules, which are too big to pass through capillary walls. A colloid solution draws fluid from the interstitial and intracellular spaces, increasing intravascular volume. The degree of osmotic pull that a colloid exerts depends on its particle concentration. Albumin and Hetastarch are examples of colloid solutions.

Question #11: Complete question #11 for ALL screened patients. Record the subjects' demographic information. Enter the year of birth or an age category if the birth year is unknown. This information can be corrected on the CRF if unknown at the time of admission to the ED.

Record subjects gender. If subject is transgendered, select the gender the subject identifies with.

Use the following race/ethnicity definitions. Check all that apply.

White, Non-Hispanic/Non-Latino: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

American-Indian/Alaska Native/Aboriginal: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black/African-American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African-American."

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin.

Native Hawaiian/Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

Other: Identifiable race/ethnicity not described above.

Note Noted/Unknown: Not able to determine the patient's race and ethnicity and no information has been recorded in the clinical record.

Source Documents: Hospital ED record or direct observation and data entry into the CRF.

Question # 12: This question is optional for screening failures. Record the subjects height and indicate the unit of measure and if the value is an estimate.

Question # 13: This question is optional for screening failures Record the subjects weight and indicate the unit of measure and if the value is an estimate.

PROPPR
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Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 1: Screening

****Based on EMS/Trauma Alert Information & Site Policies, Pre-Order Randomized PROPPR MT Blood Products If Indicated****

1. ED Arrival: Date: __ __ /__ __ __ /__ __ Time: __ __:__ __ ***(TIME ZERO)***
(dd/mmm/yy) *(24hr Clock in hh:mm)*

2 First available vital signs & GCS obtained after ED arrival:

Blood Pressure *(mmHg)*		Pulse *(beats/min)*	Temperature	Respiratory Rate
Systolic	Diastolic			
___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___ .___ ☐ F. ☐ C.	___ ___

GCS Record Component Scores **OR** GCS Total Score		Advanced Airway?	Chemically Paralyzed?
E: ___ V: ___ M: ___	GCS Total Score:___	☐ Yes ☐ No	☐ Yes ☐ No
☐ Not Recorded		☐ Unknown	☐ Unknown

3. Assessment of Blood Consumption (ABC) Score:

(Determined by Research Assistant Based on Initial Assessment on Arrival to Hospital/ED)

a. Penetrating Mechanism ☐ Yes (1) ☐ No (0) ☐ Unknown (0)

b. Systolic B/P ≤ 90 mmHg ☐ Yes (1) ☐ No (0) Time: _____:_____ *(24hr Clock in hh:mm)*

c. Pulse > 120 bpm ☐ Yes (1) ☐ No (0) Time: _____:_____ *(24hr Clock in hh:mm)*

d. FAST exam ☐ Positive (1) ☐ Negative (0) Time: _____:_____
☐ Indeterminate (0) ☐ Not Done (0) *(24hr Clock in hh:mm)*

Total ABC Score: ☐ **ZERO** ☐**1** ☐ **2** ☐ **3** ☐ **4**

4. Does ABC score predict patient will receive a MT?

☐ Yes *(ABC Score* **≥** *2,* ***Call*** *Blood Bank,* ***Process*** *TEG/Multiplate and continue to question #6)*

☐ No ***(HOLD*** *TEG/Multiplate Sample until further eligibility is determined and go to next question)*

5. Ask the Trauma Attending if a MT is needed: Time Answered: __ __:__ __
(24hr Clock in hh:mm)

☐ Yes Trauma Attending's Initials: ___ ___ ___
*(**Call** Blood Bank, **Process** TEG/Multiplate sample)*

☐ No *(Doesn't require MT. Patient is a screening failure.* ***Follow site policy on TEG/Multiplate analysis****.)*

****Patients with the 4th unit of RBC's spiked are ineligible for the PROPPR study****

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Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

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CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 1: Screening *(cont.)*

6. First Available Blood Sample: **Check here** ☐ if the blood sample was not collected & proceed to next page. Document the reason for not collecting the sample on form # 22.

Blood Draw Time *(hh:mm)*	COAGs. *(Blue Top Sodium Citrate)*			R4 Blue 4.5 mL Citrate/Benzamidine	R5 Lavender 5 mL (FLOW for CORE Lab)
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
:	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube
**Indicate if any problems occurred during collection	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**

Attach CRF Lab ID Label Here →

7. Will TEG/Multiplate lab values be reported with the first available blood sample?

☐Yes *(Record TEG/Multiplate values on form #14)* ☐ No

8. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

9. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

10. Record the total I.V. fluids & blood products infused pre-hosp. to 1st blood sample collection:

Fluid/Blood Product	Amount Infused
Normal Saline	___ ___ ___ ___ ml.
Lactated Ringers	___ ___ ___ ___ ml.
Hypertonic Solution 3%	___ ___ ___ ___ ml.
Hypertonic Solution 5%	___ ___ ___ ___ ml.
Hypertonic Solution, other %, (specify):_____	___ ___ ___ ___ ml.
Plasma-Lyte	___ ___ ___ ___ ml.
Other Crystalloids, (specify):_____	___ ___ ___ ___ ml.
Albumin (5%)	___ ___ ___ ___ ml.
Albumin (25%)	___ ___ ___ ___ ml.
Hextend	___ ___ ___ ___ ml.
Hespan	___ ___ ___ ___ ml.
Other Colloids, (specify):_____	___ ___ ___ ___ ml.
RBCs	___ ___ Units
Plasma	___ ___ Units
Platelets	___ ___ Units

Research Blood Sample Collection Problem Codes: ***a*= excessive bleeding after venipuncture, ***b***=loss of vacuum during collection, ***c***=hematoma, ***d***= Other, (describe on form #22)*

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CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 1: Screening *(cont.)*

11. Demographic Information:

a. Gender: ☐ Male
☐ Female
☐ Unknown

b. Year of Birth: ___ ___ ___ ___ □ Unknown
↓
If age is unknown, select the age group that best describes the subjects.

☐ Less than 15 years of age
☐ 15 to 19
☐ 20 to 34
☐ 35 to 49
☐ 50 to 65
☐ 65 years of age

c. Race/Ethnicity: *(Check all that apply)*

☐ White/non-Hispanic, non-Latino

☐ American Indian/Alaskan Native/Aboriginal

☐ Asian

☐ Black/African American

☐ Hispanic/Latino

☐ Native Hawaiian/other Pacific Islander

☐ Other *(Specify)*: _____

☐ Not Noted/Unknown

12. Subject height: __ __ __ . __ ☐ cm ☐ inches **Check here** ☐ if estimate

13. Subject weight: __ __ __ . __ ☐ kg ☐ pounds **Check here** ☐ if estimate

Section 3.2.2 Screening Log Instructions

Subjects meeting the sites highest level of trauma activation will be screened for eligibility to participate in the clinical trial and assigned a study ID from the screening log with the first two digits indicating the clinical site, and the remaining 5 digits sequential numbers in the order screened. The HCCC/HDCC will only receive de-identified research records/data.

PROPPR

Screening Log

Subject ID	Used By	Additional Information (Please document the reason for not using the "Subject ID" and any other additional comments)
1010001 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010002 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010003 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010004 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010005 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010006 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010007 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010008 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010009 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010010 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010011 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010012 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010013 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010014 [redacted]	☐ screen failure ☐ randomized ☐ not used	
1010015 [redacted]	☐ screen failure ☐ randomized ☐ not used	

Section 3.3 Verification of Eligibility

Section 3.3.1 Inclusion/Exclusion

To be eligible, subjects must meet ALL of the following

1) Subjects who require the highest trauma team activation at each participating center,
2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown,
3) Received directly from the injury scene,
4) Initiated transfusion of at least one unit of blood component within the first hour of arrival or during pre-hospital transport, and
5) Predicted to receive a MT by exceeding the threshold score of ***either*** the ABC score or the attending trauma physician's judgment criteria.

Subjects are ineligible if they meet one or more of the following

1) Received care (as defined as receiving a life saving intervention) from an outside hospital or healthcare facility (Procedures and care given at an outside health facility cannot be documented or controlled resulting in a high variability of standards of care and clinical outcomes.)
2) Moribund patient with devastating injuries and expected to die within one hour of ED admission; for example, those subjects with lethal traumatic brain injury deemed futile care by the neurosurgery or trauma attending prior to CT scanning or intracranial pressure monitoring, e.g. near decapitation, massive loss of intracranial contents, or transcranial gunshot wounds. Clinical assessment of severity of injury and not pupil reactivity has been found relevant in predictive models. Elderly subjects with massive myocardial infarction or stroke and severe injury based on the assessment of the trauma attending prior to randomization will also be excluded from randomization. (Those with non-survivable injuries or declared dead within 60 minutes of admission are unlikely to receive a MT.)
3) Prisoners, defined as those who have been directly admitted from a correctional facility (Prisoners are excluded because of their vulnerable population status. A free-living individual who is under police observation as a suspect will remain in the study until discharge or incarcerated.)
4) Patients requiring an emergency thoracotomy in the emergency department (Trauma patients requiring an emergency department thoracotomy have exsanguinated from large vessel injury, have an extremely high mortality and usually do not survive, irrespective of treatment.)
5) Children under the age of 15 years or under 50 kg body weight if age unknown (Subjects under 15 years of age will be excluded, as the majority of adult trauma centers consider age 15 or older to be an adult and would not admit those under age 15. However, this will allow the inclusion of subjects 15 to 17 year olds that are at a high risk of motor vehicle accidents causing blunt or penetrating injuries and are admitted to Trauma Centers.)
6) Known pregnancy in the ED (Pregnant women have a significantly increased intravascular volume and physiologic reserve for bleeding which can require adjustments to the standard treatment protocols. Therefore for consistency for data analysis, pregnant women will be excluded.)
7) Greater than 20% total body surface area (TBSA) burns (Subjects with large and severe thermal injuries will require early and aggressive resuscitation to replace intra-vascular volume losses. As such, subjects with both large TBSA burns and traumatic injuries will require a resuscitation approach that is different to current isolated trauma resuscitation strategies. Additionally, in the absence of concomitant severe blunt trauma, these subjects are unlikely to receive blood products in the early resuscitative phase.)
8) Suspected inhalation injury
9) Received greater than five consecutive minutes of cardiopulmonary resuscitation (CPR with chest compressions) in the pre-arrival or ED setting (Subjects who receive greater than five consecutive minutes of CPR in the pre-hospital or initial ED setting are more likely to have non-survivable injuries and are not likely to receive a massive transfusion. Conversely, brief episodes of CPR are not unusual in severely hypotensive subjects.)
10) Known Do Not Resuscitate (DNR) prior to randomization

11) Enrolled in a concurrent, ongoing interventional, randomized clinical trial
12) Patients who have activated the "opt-out" process or patients/legally authorized representatives that refuse blood products on arrival to ED.

Upgrades

If a patient is upgraded within the ONE hour window from time of ED arrival to the highest acuity level of and is now eligible, begin data collection and obtain research samples. Please note the ONE hour to order container and TWO hour limit to open the seal of the container are based on time of ED arrival, not time of upgrade. Thus, if the patient is upgraded after the ONE hour ED admission window, they are NOT eligible.

Transfers

If the patient is brought to an outside facility and the staff there immediately calls for the transfer without performing any care, that patient is considered a direct admit and could be considered eligible. However, *if the patient received care* at an outside facility, they are considered true transfers and would thus be deemed ineligible.

Procedural Criteria:

Subjects with a 4th unit of RBCs spiked are ineligible to be randomized in the PROPPR study. Note the 4th unit limit only applies to RBCs. It will be considered a procedural deviation if a subject is enrolled after the 4th unit of RBCs is spiked. This procedural deviation will be handled in the same manner as a protocol deviation.

Section 3.3.2 General Instructions for Completion of CRF Form # 2

Complete this form for all screened subjects. Once a subject is determined ineligible to enroll, responses to subsequent questions on the form become optional and may be left blank.

The signature block should be completed by the research team member actually completing the assessment and should be someone listed on the Sites' FDA 1572 Form.

CRF 2 will be considered the source document verifying inclusion/exclusion criteria unless site policies require a clinical note addressing each inclusion/exclusion criteria.

Inclusion Criteria Questions #1 to # 5:

Indicate if the inclusion criteria listed have been met. To be eligible, all answers must be "yes".

Source Document: Hospital ED record or direct observation and data entry into the CRF.

Exclusion Criteria Questions #1 through #12:

Indicate if any exclusion criteria listed have been met. To be eligible, all answers must be "no".

Source Document: Hospital ED record or direct observation and data entry into the CRF.

Blood Product Range Limit: Eligible subjects must have received 1 unit of blood products within 1 hour of admission or during pre-hospital transport. However, subjects with a 4^{th} unit of RBC's spiked are ineligible to randomize in the PROPPR MT protocol. Note the 4 unit limit applies only to RBC's.

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Form 2: Verification of Eligibility

Inclusion Criteria: *(To be eligible, all questions must be answered "**YES**")*

1. Subject requires highest level of trauma activation	☐ Yes	☐ No
2. Age (Est. ≥ 15 yr. or ≥50 kg if age unknown)	☐ Yes	☐ No
3. Received directly from the injury scene	☐ Yes	☐ No
4. Received at least 1 unit of a blood component within the 1st hour after arrival or during pre-hospital transport	☐ Yes	☐ No
5. Predicted to receive a MT by exceeding the ABC threshold score or the Trauma Attending's judgment	☐ Yes	☐ No

Exclusion Criteria: *(To be eligible, all questions must be answered **"NO"**)*

1. Received care (defined as receiving a lifesaving intervention) from an outside hospital or healthcare facility	☐ Yes	☐ No
2. Moribund patient with devastating injury or expected to die within 1 hour of ED admission	☐ Yes	☐ No
3. Prisoners, defined as those who have been directly admitted from a correctional facility	☐ Yes	☐ No
4. Patients requiring an emergency thoracotomy (in ED)	☐ Yes	☐ No
5. Children under the age of 15yrs or under 50kg if age unknown	☐ Yes	☐ No
6. Known pregnancy in ED	☐ Yes	☐ No
7. Burns > 20% TBSA	☐ Yes	☐ No
8. Suspected inhalation injury	☐ Yes	☐ No
9. CPR (chest compressions for > 5 consecutive minutes) in the pre-arrival or ED setting	☐ Yes	☐ No
10. Known Do Not Resuscitate (DNR) prior to randomization	☐ Yes	☐ No
11. Enrolled in another concurrent, ongoing interventional, randomized clinical trial	☐ Yes	☐ No
12. Patients who have activated the "opt out" process or patients Legally Authorized Representatives that refuse blood products on arrival to ED.	☐ Yes	☐ No

Procedural Criteria: *(To be eligible, must be answered **"NO"**)*

1. At time of eligibility assessment, the 4th unit of RBC's was spiked.	☐ Yes	☐ No

Patient Eligibility Verified by:

_____ _____ _____:_____

Print Name *Signature* *(24hr Clock in hh:mm)*

Chapter 4 – EMS/Pre-hospital Care

Section 4.1 Overview

Prehospital EMS data will be collected to verify inclusion criteria. Complete this entire form for all randomized subjects. Only complete questions 1-7 for screen failures who have had a research blood sample collected.

Section 4.2 General Instructions for Completing the EMS/Pre-hospital CRF Form #3

Question #1: Enter the EMS call date in dd/mmm/yy format. EMS call date is defined as the date when the EMS service was notified of the trauma. If EMS was not used, select "na" and proceed to question #5 on the form.
Source Documents: EMS record, Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from the EMS provider while in the ED).

Question #2: Enter the EMS call dispatch time in hh:mm. The EMS dispatch call time is defined as the time when the EMS service was notified of the trauma. Indicate if the time is an estimate or if no information is available, leave the field blank and select not noted/unknown.
Source Documents: EMS record, Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from the EMS provider while in the ED).

Question #3: Enter the EMS arrival time at the scene of the accident in hh:mm. Indicate if the time is an estimate or if no information is available, leave the field blank and select not noted/unknown.
Source Documents: EMS record, Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from the EMS provider while in the ED).

Question #4: Enter the first available vital signs and Glasgow Coma Score (GCS) obtained by EMS at the scene of the accident. Select the unit of measure for temperature. Use the following key for GCS scoring. Record the total GCS if component scores are unavailable.

GCS Scoring Key

Eye Movement (E)		Verbal (V)		Motor (M)	
1	No Response	1	No Response / Intubated	1	No Response
2	To Pain	2	Incomprehensible Sounds	2	Extension *(Decerebrate)*
3	To Verbal Command	3	Inappropriate Words	3	Flexion – *(Decorticate)*
4	Spontaneous	4	Disoriented, Converses	4	Flexion – Withdrawals From Pain
		5	Oriented, Converses	5	Localizes Pain
				6	Obeys Commands Appropriately

Indicate if the patient had an advanced airway at the time the verbal GCS component was assessed. For the purpose of GCS, the verbal score should be "1" in the presence of an advanced airway. Advanced airway is defined here as a device used as a method to assist and/or control ventilation. These devices mechanically prohibit verbal response testing. Devices used to assist and/or control ventilation are: bag value mask, oral ET, nasal ET, Combitube, LMA, King Airway, and cricothyrotomy/tracheostomy.

Indicate if the patient was chemical paralyzed at the time of the assessment. Paralytic drugs are defined as Pancuronium Bromide, Rocuronium, Succinylcholine, or Vercuronium.

Source Documents: EMS record, Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from the EMS provider while in the ED).

Question #5: Indicate how the patient was transported to the ED. If "other" is selected, record the information on form # 22.
Source Documents: Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from the EMS provider while in the ED).

Question #6: Indicate the mechanism of injury, selecting all that apply. If "other" is selected, record the information on form # 22.
Source Documents: EMS record, Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from a healthcare provider while in the ED).

Question #7: Indicate if any pre-hospital life-saving interventions were performed, select all that apply.
Source Documents: Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from a healthcare provider while in the ED).

Question #8: Record the amount of IV fluids or blood products the patient received before ED arrival. If "other" is selected, record the information on form # 22.
Source Documents: Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from a healthcare provider while in the ED).

Crystalloids vs. Colloids

Crystalloids are fluids that contain a combination of water and electrolytes. Common examples are NS, LR, D5W, D51/2 NS, D5 ¼, NS and Plasmalyte. Crystalloid solutions closely mimic the body's extra cellular fluid. Given I.V., crystalloid solutions diffuse through the capillary walls that separate plasma from interstitial fluid. They can be used to expand both intravascular and extra vascular fluid volume.

Colloids are fluids that contain dissolved particles, such as protein, sugar, and starch molecules, which are too big to pass through capillary walls. A colloid solution draws fluid from the interstitial and intracellular spaces, increasing intravascular volume. The degree of osmotic pull that a colloid exerts depends on its particle concentration. Albumin and Hetastarch are examples of colloid solutions.

Question #9: Indicate if the patient received a procoagulant medication before ED arrival. Procoagulant medications used by EMS include Prothrombin Complex Concentrate (PCC), and Tranexamic Acid (Cyclokapron). If "other" is selected, record the information on form # 22.
Source Documents: Hospital ED record or direct observation and data entry into the CRF, (i.e. the coordinator obtained the information from a healthcare provider while in the ED).

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Form 3: EMS / Pre-Hospital Care

1. EMS call date: __ __/__ __ __/__ __, ☐ NA, EMS Not Used *(Go to question #5 below)*
   (dd/mmm/yy)

2. EMS call/dispatch time: ____:____ ☐ Not Noted/Unknown
   (24hr Clock in hh:mm)

3. EMS arrival at scene: ____:____ ☐ Not Noted/Unknown
   (24hr Clock in hh:mm)

4. First available vital signs & GCS obtained by EMS at the scene:

Blood Pressure *(mmHg)*		Pulse *(beats/min)*	Temperature	Respiratory Rate
Systolic	Diastolic			
___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___ .___ ☐ F ☐ C	___ ___

GCS		Advanced Airway?	Chemically Paralyzed?
Record Component Scores **OR** GCS Total Score			
E: ___ V: ___ M: ___	GCS Total Score:___	☐ Yes ☐ No	☐ Yes ☐ No
☐ Not Recorded		☐ Unknown	☐ Unknown

5. Method of arrival to hospital: *(Select one)*

   ☐ Ambulance ☐ Helicopter/Air Transport ☐ Private Vehicle
   ☐ Walk in ☐ Other, describe: _____

6. Mechanism of Injury: (*As ascertained by EMS*)

   a. ☐ **Blunt Injury** *(Select all that apply)*
   - □ Fall
   - □ Machinery
   - □ MVC – Occupant
   - □ Motorcycle
   - □ MVC – Motorcycle
   - □ MVC – Bicycle
   - □ MVC – Pedestrian
   - □ Other, *(Describe)*:_____
   - □ MVC – Unknown
   - □ Struck by/against (assault)
   - □ Bicycle

   b. ☐ **Penetrating Injury** *(Select all that apply)*
   - □ Gunshot Wound
   - □ Stabbing (knife)
   - □ Shotgun Wound
   - □ Other, (*Describe*): _____
   - □ Impalement

7. Did the subject receive any pre-hospital lifesaving interventions?

   ☐ Yes, (*Select all that apply*) ☐ No
   - □ Cardioversion
   - □ Intubation
   - □ Chest/Needle Decompression
   - □ Trach/Cricothyrotomy
   - □ CPR
   - □ Tourniquet

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Study ID # ___ ___ ___ ___ ___ ___ ___

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CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 3: EMS / Pre-Hospital Care *(continued)*

8. IV fluids and/or blood products given before ED arrival:

Record total volume infused, **or check here** ☐ if no IV fluids/blood products were given.

Fluid/Blood Product	Amount Infused
Normal Saline	___ ___ ___ ___ ml.
Lactated Ringers	___ ___ ___ ___ ml.
Hypertonic Solution 3%	___ ___ ___ ___ ml.
Hypertonic Solution 5%	___ ___ ___ ___ ml.
Hypertonic Solution, other %, *(Specify)*:_____	___ ___ ___ ___ ml.
Plasma-Lyte	___ ___ ___ ___ ml.
Other Crystalloids, *(Specify)*:_____	___ ___ ___ ___ ml.
Albumin (5%)	___ ___ ___ ___ ml.
Albumin (25%)	___ ___ ___ ___ ml.
Hextend	___ ___ ___ ___ ml.
Hespan	___ ___ ___ ___ ml.
Other Colloids, *(Specify)*:_____	___ ___ ___ ___ ml.
RBCs	___ ___ Units
Plasma	___ ___ Units
Platelets	___ ___ Units

9. Procoagulants given before ED arrival?

Record total dose, **or check here** ☐ if no procoagulant were given before ED arrival.

Prothrombin Complex Concentrate *(PCC)*	Dose: ___ ___ ___ *(Specify Unit of Measure:_____)*
Tranexamic Acid *(Cyclokapron)*	Dose: ___ ___ ___ *(mg/kg/hr.)*
Other Procoagulant, *(Specify)*:_____	Dose: ___ ___ ___ *(Specify Unit of Measure:_____)*

Chapter 5 - Randomization of Blood Products at the Blood Bank

Section 5.1 Overview

This section will cover the randomization process for the blood products in the PROPPR trial. Section 5.3 includes a detailed Blood Bank flow chart of the process as does the recording of the Transfusion Webinar on this topic, which can be viewed via the PROPPR sharepoint website <insert PROPPR sharepoint access>

Section 5.1.1 Availability of Blood Product & Treatment Assignment Labels

In cases where products for all treatment groups are unavailable for transfusion, the blood bank will indicate the patient cannot be randomized into the trial. A site cannot randomize if there is not enough product in the blood bank for BOTH treatment arms. The blood banks should have at least enough products available for 2 containers of 1:1:1 ratio – i.e. 12 RBCs, 12 plasma, and 2 platelets. This amount of products should be enough to also fill 2 containers for the 1:1:2 group.

Supply should be checked daily and if there are not enough products to randomize a patient the blood bank should notify the PROPPR research coordinator.

A site must also have randomization numbers available via the treatment assignment labels that will be sent to them from the HDCC.

Section 5.2 Blood Bank Notification to Randomize a Subject

The Blood Bank will be notified by a clinical staff member to randomize blood products for a potential subject.

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Blood Bank Randomization Process

Blood Bank Notified of PROPPR MT Subject & Provided Study ID Number

Blood Bank Opens PROPPR Randomization Log. 1st Available Randomization Number/Treatment Group Assigned to Subject and Recorded in Log

Transport Container Delivered **Within 10 Minutes** of Notification

Blood Bank Randomizes Subject to Group

1:1:1 Treatment Group

1:1:2 Treatment Group

Blood Transport Container Prepared. Randomization Number Attached With Platelets & Sealed

Blood Transport Container Prepared. Randomization Number Attached With Sham Platelets & Sealed

Subjects Who Do Not Receive PROPPR MT Products **Within 2 Hrs.** of Arrival to ED Will Be Considered Screening Failures

Sealed Blood Transport Container Delivered to Subject Location

Blood Bank Immediately Prepares/Delivers Next Transport Container of PROPPR Blood Products Per Assigned Group

First Blood Transport Container Returned to Blood Bank

Was the Transport Container Seal Broken?

NO

Randomization Number Returned to Master Log & Available for Next Subject

YES

Were Any PROPPR MT Blood Products Given?

NO

Blood Bank Informs Research Team Transport Container Seal Broken, **Confirming Subject is Enrolled in PROPPR Study**

Blood Bank or Study Coordinator Notifies HDCC of Randomization Number Assignment

Blood Bank Enters Randomizaton Information into Master Subject Log

Section 5.4 Obtaining Treatment Assignment and the Treatment Assignment Label Packet

The HDCC will send a set of randomization labels (10 randomization numbers and assignments at a time) to the contact person at the blood bank at each site in a plastic sheet.

Figure 1 below is a picture of the Blood Bank Randomization stickers.

The 10 numbers and assignments will arrive via FedEx from the HDCC in 2 clear plastic sheets (note 5 unique numbers per sheet) with two columns of the same numbers. When a site is nearing the end of their list the HDCC will send the next batch of 10 numbers in clear plastic sheets. It is important that these treatment assignment labels are kept in a locked and secure place within the blood bank so that a site clinical investigator or coordinator does not accidentally see the labels.

Figure 1

Labels in this column go on the Master log ONLY if a patient is randomized and enrolled in PROPPR. If blood products are returned, label remains in slot on sheet.

Labels in this column go in the platelet or sham platelet container sent to the bedside. If patient is not randomized and enrolled in PROPPR, product is returned and label is put back in the slot on the sheet, ready for the next platelet container.

Section 5.5 Preparing Randomized Blood Product Transport Containers

1. Blood Bank receives notification of PROPPR activation and records information pertinent to MTP activation per site specific instructions. Information may include the following based on your site's specifications:
    a. Patient name and MRN
    b. Time and date of activation
    c. Name of person providing information
    d. Name of physician activating PROPPR
    e. Location of patient
    f. Estimated arrival time in blood bank for patient sample

2. Blood Bank randomizes product for the PROPPR blood product containers
    a. randomization number and assignment selected from next line in PROPPR treatment assignment label sheet.

3. Blood Bank prepares **1st container** of blood products for PROPPR.
    a. **1:1:1 ratio (1st container has 1 platelet, and 6 RBCs, 6 plasma)**
        - Platelet has tag "TRANSFUSE PLATELETS FIRST" attached to unit
    b. Platelet placed in platelet container and attached to 1st container. Blood Bank communicates randomization number and assignment to Clinical Research Staff by

putting label with the randomization number inside the 1st platelet container (kept at room temperature).

- Remainder of blood products are placed in container that can maintain cool temperature.
- Container for platelets and for other blood products sealed and transported to patient's location

c. **1:1:2 ratio (1st container has 6 RBCs, 3 plasma, No platelet issued with 1st container** so dummy platelet placed in platelet container along with randomization sticker)

- Container for sham platelets and for other blood products are sealed and transported to patient's location

4. Blood Bank prepares **2nd container** of blood products for PROPPR
   a. **1:1:1 ratio (2nd and all successive containers identical to 1st with 1 platelet, 6 RBCs, 6 plasma)**
      - Platelet has tag "TRANSFUSE PLATELETS FIRST" attached to unit.
      - Platelet placed in platelet container
      - Container of blood products is transported to patient's location
   b. **1:1:2 ratio (2nd and every even round of PROPPR MTP 1:1:2 ratio has platelet issued with plasma and RBCs).**
      - **2nd and all even numbered containers have 1 platelet, 6 RBCs, 3 plasma**
      - Platelet has tag "TRANSFUSE PLATELETS FIRST" attached to unit
      - Platelet placed in platelet container
      - Container transported to patient's location
   c. **1:1:2 ratio 3rd and every odd round of PROPPR 1:1:2 ratio has no platelet issued with plasma and RBCs**
      A. 3rd and all odd numbered containers have 6 RBCs and 3 plasma
      - Container transported to patient's location

5. Successive containers prepared and issued upon demand until Blood Bank is notified PROPPR discontinued
   a. 1:1:1 ratio – every container has 1 platelet, 6 RBCs, 6 plasma
   b. 1:1:2 ratio – all odd numbered containers have 6 RBCs, 3 plasma
   c. 1:1:2 ratio – all even numbered containers have 1 platelet, 6RBC, 3 plasma

6. ***If patient not randomized by Trauma Team***
   1st container of blood components returned with seal intact
   1. Blood Bank returns blood components per standard SOP
   2. Patient's protocol study identification number removed from site blood bank records
   3. **Randomization number label with treatment assignment returned to randomization sheet for use with next potential PROPPR protocol patient.**
   4. **Failure to use the returned and unused study number on the next patient disrupts the randomization of the study. Please refer to the misrandomization Section 5.7.**

Section 5.5.1 Sham Platelet Process

In PROPPR it is not practical to blind the investigators to treatment assignment during administration of the treatment or even more impractical the construction of the containers. However, we are attempting to blind the investigating clinical team from treatment assignment right up until the point in which they decide to "break the seal" and randomize the patient into PROPPR.

To accomplish this we are sealing the containers and introducing sham platelet should the container need them. The shams are used to prevent unblinding of investigators prior to making the decision to randomize. They are needed in the event that a container's contents could be detected in the absence of platelets, since no platelets would indicate that the contents of the container would be in the 1:1:2 Group. The site's containers require shams for blinding up until the point of patient randomization. The shams are constructed so there is no chance that it will be given to a patient and designed to mimic the containers of platelets in weight and visual appearance.

If platelet sham needs improvement and type of sham is changed, we ask that you call the HDCC (may require sending pictures of new versions for evaluation) before using.

	Container 1	Container 2	Successive containers…
1:1:1 (Group 1)	 6 RBCs  6 Plasma  1 Platelet + Treatment Assignment label in platelet container 	 6 RBCs  6 Plasma  1 Platelet	Same as Container 2
1:1:2 (Group 2)	 6 RBCs  3 Plasma + Treatment Assignment label in platelet container 	 6 RBCs  3 Plasma  1 Platelet	Odd numbered containers (i.e., 3, 5, 7, …) same as container 1 (without a label) Even numbered container (i.e., 4, 6, 8, …) same as container 2

Section 5.5.3 Sealing the Blood Transport Container

The type of seal needed on the blood product container depends on the type of blood product container used at the site. 2 seals will be needed on the entire container in the event a site is using a container that requires a seal on the refrigerated container and the platelet container separately.

If container and/or platelet lock is changed, we ask that you send HDCC pictures of new versions for evaluation before using.

Section 5.5.4 Delivery of Blood Transport Container/Preparation of Next Container

How a blood product container is delivered to the bedside is site specific. However in each case it is important that the containers are constructed as indicated above and that they continue in the assignment the patient has been randomized too until the blood bank is notified by the clinical staff to discontinue product delivery.

Section 5.6 Returned Blood Transport Containers

Section 5.6.1 Inspecting Blood Transport Container Seals

Once the container is returned to the blood bank, the blood bank personnel will inspect the seal (or seals) to see if they are broken. In the event a site is using a container that requires a seal on the refrigerated container and the platelet container separately, if either of the container seals are broken the patient is randomized.

Section 5.6.2 Procedure for Unbroken Seals (return blood products to inventory and treatment assignment label to packet)

If the seal is unbroken, the blood products will be returned to their appropriate storage location, the subject's randomization number and treatment assignment label will be returned to the randomization list (returned to the original place in the plastic sheet), so that the next eligible subject will receive the same blood product assignment.

Section 5.6.3 Procedure for Broken Seals (Record Randomization of Subject in BB Master Subject log)

If the seal on the container is broken, for any reason, the subject is randomized into the assigned treatment group. The blood bank will call to confirm with the research staff that the patient has been randomized. The blood bank personnel will then affix the label of the second of the two treatment assignment labels with the randomization number (the label immediately next to it in the plastic sheet) to the PROPPR Blood Bank Randomization log.

The PROPPR blood bank randomization log will be given to each of the blood banks at the site to complete. Below is an example of the Blood Bank Randomization Record. Additional blank sheets of the blood bank log will be available for printing at the PROPPR Sharepoint site.

It is important to note that this log should not be used for tracking returned containers, it is only for logging the randomized products and treatment assignment numbers for patients who are randomized and thus enrolled in the trial.

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PROPPR Blood Bank Subject Master Log

Date Notified of PROPPR MT Subject	Patient Name & Medical Record Number	PROPPR Randomization Number	Randomized?	
____ / ____ / ____			☐ Yes	☐ No *(Reuse Number)*
____ / ____ / ____			☐ Yes	☐ No *(Reuse Number)*
____ / ____ / ____			☐ Yes	☐ No *(Reuse Number)*
____ / ____ / ____			☐ Yes	☐ No *(Reuse Number)*
____ / ____ / ____			☐ Yes	☐ No *(Reuse Number)*

Section 5.7 Misrandomization

In the rare event that the blood bank misrandomizes a patient (for example: takes an entry out of sequence on the list or fails to reuse a number when the product is returned) we will include the patient in all analyses and analyze the patient "as randomized so analyzed". To further limit the potential frequency and impact of this type of protocol deviation we intend to give the blood bank a minimum number of treatment assignments (no more than 10 numbers) and we have sequentially numbered the randomization numbers.

Section 5.7.1 Return of Randomization Lists

A misrandomization is considered a failure to follow the protocol and the site will need to obtain a new randomization list. This new list is supplied to the site (with a corrected randomization number replacing the number given to the misrandomized patient). Every effort must be made to keep this number small.

To expedite the receipt of a new randomization list, so that the site may continue to randomize patients, the research team and the blood bank personnel should immediately call 713-500-9550 OR 1-855-244-8593 emergency HDCC line to indicate a misrandomization has occurred. The HDCC representative who receives the call will place a new set of labels in FedEx and email the tracking number to the site. Then the site will place the old list in a FedEx package (containing the remaining assignments) and email the HDCC (at proppr@uth.tmc.edu) the FedEx tracking number of the returning old list. The emergency line should only be called in the case of a misrandomization. For all other non-emergency technical or procedural questions please call 713-500-9512 (Sarah Baraniuk, PhD., HDCC Co-PI) or 713-500-9576 (Josh Nixon HDCC Data Research Associate).

While the site is waiting on the new list to arrive the HDCC representative will email the first two randomization numbers from the list that is in the FedEx packet for the site to use if they need to randomize while the FedEx is enroute. If the emergency number is used, take one of the emergency labels provided with the original packet (blank pink sticker without a bar code), write the randomization number and assignment on the labels for placing in the platelet container and the Blood Bank log.

As soon as the FedEx is delivered the Blood Bank personnel should call (using the 713-500-9550 OR 1-855-244-8593 emergency line) the HDCC directly and remove any randomization numbers and assignments that were used from the plastic sheets so that there is no chance that they could be used again (causing another misrandomization).

Section 5.7.2 Ineligible Patients Who Receive Treatment (Emergency Use)

If PROPPR container products are given to a patient who was determined to be ineligible before randomization (before the container seal was broken), then this patient will be considered a screen failure. The blood bank must be informed to call the HDCC as this will require reissuing another randomization list to the site, using the instructions as listed above in Section 5.7.1.

If the patient was determined to be ineligible after the container seal was broken (after a randomization has occurred) the subject will be included in the intent to treat analysis and followed for safety and mortality endpoint assessment.

See flowchart on the next page for further clarification.

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Emergency Use, Randomization, and Determination of Ineligibility Flow Chart

****REMINDER****

Up to 3 units of RBC'S can be given before breaking the blood transport container seal. Ensure no other blood products are available prior to breaking the seal for emergency use.

Was ineligibility determined after the seal was broken?

- **No** → **Was the seal broken due to emergency need for blood products?**
  - **Yes** → Subject is a screening failure.

    Report occurrence to the HDCC (1-855-244-8593), and submit an occurrence report form.

    A new randomization list will be sent to the blood bank.
- **Yes** → Patient is a randomized subject.

  Stop PROPPR protocol and continue transfusions per standard of care.

  Do not collect any further research lab samples.

  Monitor subject for AE/SAE'S and mortality data (24hr / 30 day).

  Complete CRF forms for data collected up to the point ineligibility was determined, (most likely CRF forms # 1 through 4, 6, 7, 12, 14, 17, 18, and 22).

  Submit occurrence report form to the HDCC. Follow local IRB reporting procedures.

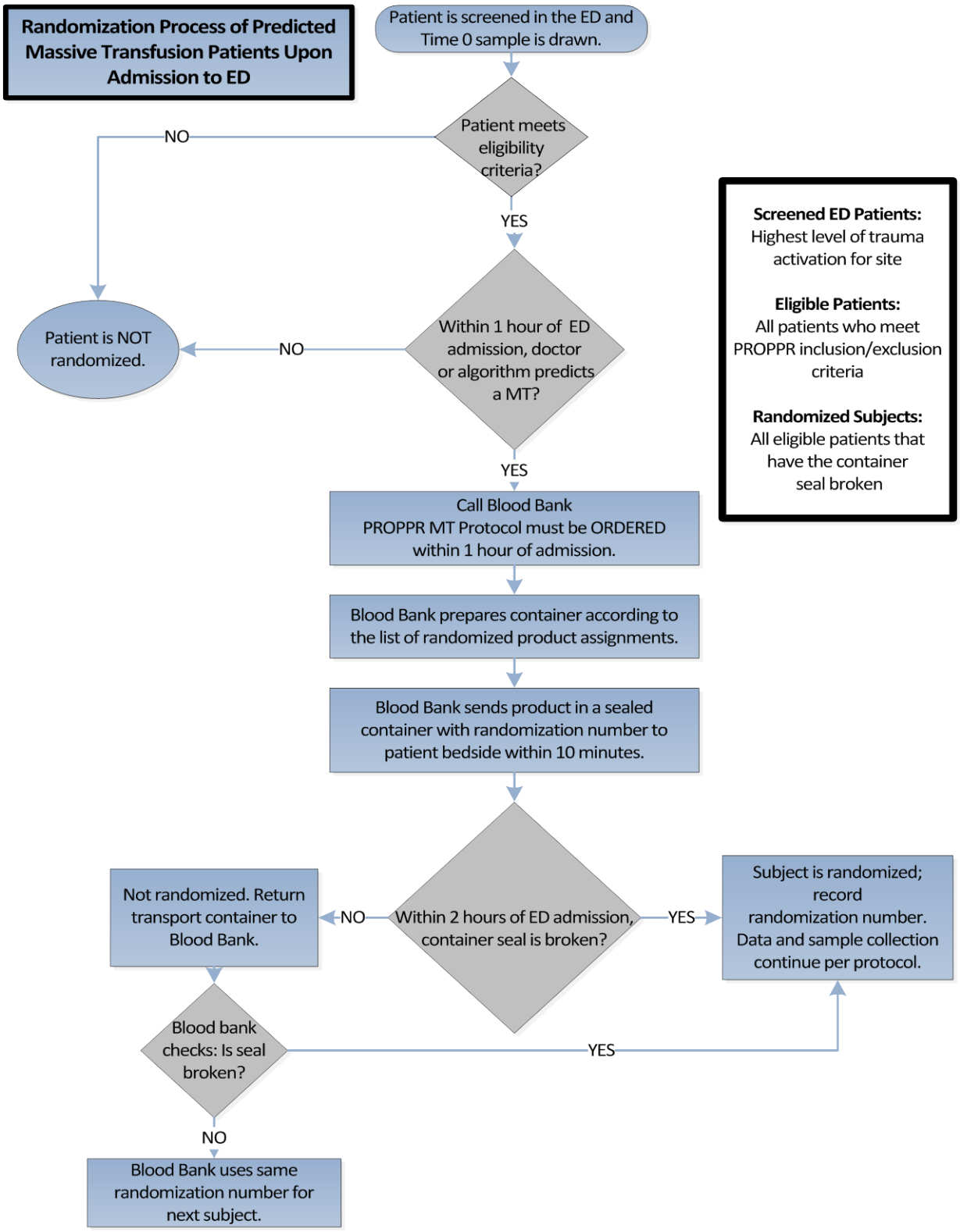
  Blood bank will continue to use current randomization list.

DOCUMENT VERSION DATE: 26OCT2012

Chapter 6 - Study Intervention (Randomization and Treatment of Patient)

Section 6.1 Overview

Section 6.1.1 Randomization Diagram



Section 6.2 Definition of Randomization

A patient is randomized and enrolled into the PROPPR trial when a container seal is broken. In the event a site is using a container that requires a seal on the refrigerated container and the platelet container separately, if either of the container seals are broken the patient is randomized.

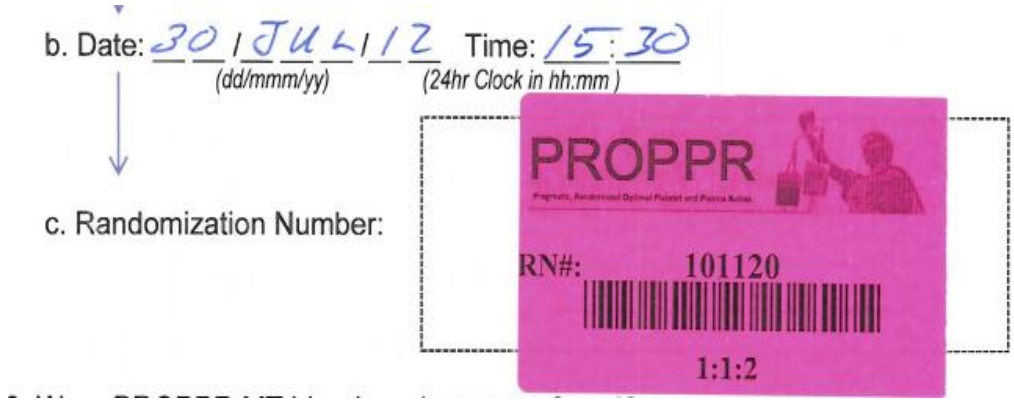
Section 6.3 Randomization of the Patient

Section 6.3.1 General Instructions for Form #4: Randomization

Complete this form for all screened subjects who have met inclusion/exclusion criteria on form #2.

Question #1: Indicate if PROPPR MT blood products were ordered from the blood bank. If PROPPR MT blood products were not ordered, select "no" and indicate a reason. If "other" is selected as a reason for not ordering blood products, record the information on form # 22. The patient will be considered a screening failure. If PROPPR MT blood products were ordered, enter the time of the **initial** telephone call to the blood bank and the time the **first** PROPPR blood products were received in hh:mm. At some sites *(if permitted by institutional policies)*, the times entered may be earlier than the patient ED arrival time.
Source Documents: Direct observation and data entry into the CRF.

Question #2: The first PROPPR blood products issued from the blood bank will be sealed. Indicate if the seal was broken on the blood transport platelet container. If the seal was **not** broken, select "no" and indicate a reason. If "other" is selected, record the information on form # 22. The patient will be considered a screening failure. If yes is selected, enter the date and time in dd/mmm/yy and hh:mm formats. Attach the randomization number label provided by the blood bank in the space provided.



The blood bank will issue randomization numbers in an assigned order. Once the seal is broken, the patient is considered randomized and in the PROPPR study, regardless of whether any blood products are actually given. Randomization numbers cannot be reused once assigned.
Source Documents: Direct observation and data entry into the CRF.

Question #3: Indicate if any PROPPR MT blood products were given. If "no" is selected, indicate the reason. If "LAR declined" is selected, provide additional documentation on forms 19 & 20. If "No" was selected for any reason, check the box at the beginning of CRF 7 to indicate there was no end of resuscitation data to record.
Source Documents: Direct observation and data entry into the CRF.

Question #4: Indicate the patient location where PROPPR MT Protocol was started. The PROPPR MT "start time" is defined as breaking the seal on the blood transport containers. If "other" is selected, record the information on form # 22.
Source Documents: Direct observation and data entry into the CRF.

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Study ID # ___ ___ ___ ___ ___ ___ ___ **(Bar Code)**

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CRF Version Date: 2013 MAR 01 Completed By: ___ ___ ___

Form 4: Randomization

1. Were PROPPR MT blood products ordered?

a. ☐ Yes ☐ No → *Reason?* ☐ Subject Died ☐ PROPPR Blood Products Not Available
↓ ☐ Other: _____

b. Time Blood Bank Notified of 1st PROPPR MT Order: __ __:__ __
↓ *(24hr Clock in hh:mm)*

c. Time 1st PROPPR Blood Products Received at the bedside: __ __:__ __
(24hr Clock in hh:mm)

2. Was the seal broken on PROPPR blood transport container?

a. ☐ Yes ☐ No →*Reason?*
- □ Subject Died
- □ Subject Improved, MT not needed
- □ Further Care Futile
- □ Screening failure, no PROPPR MT products were given within the 2hr window from admission.
- □ Screening failure, received 4 or more units of RBCs before subject could be randomized into the PROPPR study.
- □ Physician refused to randomize subject.
- □ Other, *(Specify)*: _____

b. Date: __ __ /__ __ __ /__ __ Time: ____:____
(dd/mmm/yy) *(24hr Clock in hh:mm)*

c. Randomization Number:

Record or Attach the Randomization Number Provided by Blood Bank Here

___ ___ ___ ___ ___ ___

3. Were PROPPR MT blood products transfused? (*If "**NO**" is selected for any reason, check the box at the beginning of form #7 to indicate there is no end of resuscitation data to record.*)

☐ Yes ☐ No → *Reason?*
- □ Subject Died
- □ Subject Improved, MT not needed
- □ Further Care Futile
- □ LAR Declined (*Document on forms 19 &/or 20*)

4. Where was PROPPR MT protocol started? *(Select one)*

☐ ED ☐ OR ☐ IR ☐ ICU ☐ Intermediate Level Care

☐ Nursing Unit ☐ Other, *(Specify)*:_____

Section 6.4 Administering Randomized Blood Products (See also reference to PROPPR IB/AABB Blood Guide)

Section 6.4.1 Recommended Process

- The goal for delivery of the first container is 10 minutes after blood bank is notified.
- Once the container seal has been broken, notify the blood bank so they are aware that the patient has been randomized and seal has been broken so they can continue to send study specific containers with the assigned ratio group
- Universal donor products may be used for the study containers until ABO)/type-specific products are available.
- Study blood products can be given simultaneously or serially (platelets then RBC then plasma).
- Platelets should be given first and the randomization number label for the CRF is placed in the Platelet container.
  – for the 1:1:1 ratio group, platelets should be given first
  – for the 1:1:2 ratio group, platelets should be given before or with the 7th unit of RBCs
- All products from the first study container must be given before products from the second container are given.
- Crystalloid and artificial colloid fluid can be used but are NOT to be a part of the randomization process for PROPPR – the type and amount of fluid given will be documented on the case report forms.
- Pharmacological adjuncts (such as rFVIIa, amicar, transexamic acid, and fibrinogen) and cryoprecipitate can be used but are NOT be a part of the randomization process for PROPPR – their use will be documented on the case report forms.
- During the time frame when the study blood products are given, **NO ADDITIONAL** blood products should be given (for example, cannot order extra plasma if the physician wants to give one more unit of plasma). In the event that the subject's condition necessitates an alteration in how the study products are given, the study protocol should be stopped and standard of care procedures initiated. The PI should then notify the HDCC/HCCC why the protocol was called off prior to one of the 3 reasons for stopping the PROPPR MT protocol.
- If the blood bank does not have all products available, the blood bank will notify the research staff and the patient will not be randomized into the trial.
  (The blood banks should have at least enough product available for 2 containers of 1:1:1 ratio – i.e. 12 RBCs, 12 plasma, and 2 platelets) as this would also allow two containers of 1:1:2.
- Please make sure the study container seals are not broken by the clinical staff so they can verify the products before they are used. If the seal is broken FOR ANY REASON, the patient is considered in the study.
- If your site is utilizing the Belmont, the blood products should be hung and spiked in the order depending on the group the subject has been randomized to (1:1:1 or 1:1:2).

*** Please note that the information in this section of the manual does NOT replace the SOPs in place at your institution. This information is to assist with clarification of the use of the products during the PROPPR study.

Group 1

1:1:1 Ratio, Blood Products Administration Tool

1st Blood Transport Container: Give Products in the Following Order.

- ☐ Platelets
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma

2nd Blood Transport Container: Give Products in the Following Order.

- ☐ Platelets
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma

3rd Blood Transport Container: Give Products in the Following Order.

- ☐ Platelets
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma

4th Blood Transport Container: Give Products in the Following Order.

- ☐ Platelets
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma
- ☐ RBCs
- ☐ Plasma

Continue Transfusion Sequence Until End of PROPPR MT Resuscitation

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Group 2

1:1:2 Ratio, Blood Products Administration Tool

1st Blood Transport Container: Give Products in the Following Order.	2nd Blood Transport Container: Give Products in the Following Order.	3rd Blood Transport Container: Give Products in the Following Order.	4th Blood Transport Container: Give Products in the Following Order.
□ RBCs	□ Platelets	□ RBCs	□ Platelets
□ RBCs	□ RBCs	□ RBCs	□ RBCs
□ Plasma	□ RBCs	□ Plasma	□ RBCs
□ RBCs	□ Plasma	□ RBCs	□ Plasma
□ RBCs	□ RBCs	□ RBCs	□ RBCs
□ Plasma	□ RBCs	□ Plasma	□ RBCs
□ RBCs	□ Plasma	□ RBCs	□ Plasma
□ RBCs	□ RBCs	□ RBCs	□ RBCs
□ Plasma	□ RBCs	□ Plasma	□ RBCs
	□ Plasma		□ Plasma

Cooler #1, #2, #3, #4

☐ 1. Platelets 

☐ 2. RBC 

☐ 3. Plasma 

☐ 4. RBC 

☐ 5. Plasma 

☐ 6. RBC 

☐ 7. Plasma 

☐ 8. RBC 

☐ 9. Plasma 

☐ 10. RBC 

☐ 11. Plasma 

☐ 12. RBC 

☐ 13. Plasma 

Cooler #1, #3	Cooler #2, #4
☐ 1. RBC 	☐ 1. Platelets 
☐ 2. RBC 	☐ 2. RBC 
☐ 3. Plasma 	☐ 3. RBC 
☐ 4. RBC 	☐ 4. Plasma 
☐ 5. RBC 	☐ 5. RBC 
☐ 6. Plasma 	☐ 6. RBC 
☐ 7. RBC 	☐ 7. Plasma 
☐ 8. RBC 	☐ 8. RBC 
☐ 9. Plasma 	☐ 9. RBC 
	☐ 10. Plasma 

Section 6.5 End of Resuscitation/PROPPR Treatment

Once the study container seal has been broken and the subject is receiving PROPPR study products per the assigned ratio group, the PROPPR MT protocol will continue until one of the following:

1) PROPPR transfusion protocol has been discontinued by the trauma attending because hemostasis has been achieved (hemostasis is defined in section 6.5.1)
2) The subject has died
3) The patient or legally authorized representative (LAR) refuses consent to continue participation in the trial

Section 6.5.1 Hemostasis Definitions

Definition of Anatomic hemostasis

Surgeon declares hemostasis, based on the following objective criteria

- No bleeding requiring intervention in the surgical field
- In the IR suite, resolution of blush after embolization

Definition of when Active Resuscitation stops after anatomic hemorrhage control

Based on hemorrhage control criteria above, hemostasis is complete

Surgeon and/or anesthesiologists agree that patient is adequately resuscitated, based on the following criteria, if available:

- Stable or increasing blood pressure, or
- Stable or decreasing heart rate, or
- Stable or increasing urine output, or
- Decreasing requirement for pressors to maintain a stable blood pressure

Actions to be taken when both anatomic and physiology criteria are met

Surgeon and/or anesthesiologists stops the MT protocol (calls the blood bank and stops the transfusion)

All blood products and fluids received after active resuscitation stops (but within 24 hours of admission) will be recorded as post resuscitation fluid and will be given based on local practice.

Suggested Script for Asking if Hemostasis has Been Acheived

Anatomic Hemostasis:

The CeTIR research assistant will ask the surgeon BEFORE the end of the procedure in the OR or IR:
Dr._____, Have you achieved hemostasis?
If the answer is yes, anatomic hemostasis has occurred. You will need to document the date and time of anatomic hemostasis. If the answer is no, you will need to ask the question prior to the surgeon departing the OR or IR suite.

Endpoint of Active Resuscitation After Anatomic Hemostasis:

If anatomic hemostasis has been achieved the CeTIR research assistant will ask the surgeon and anesthesiologist if the Pt. has been adequately resuscitated in the OR or IR suite:
Dr. (surgeon)_____ and Dr. (anesthesiologist)_____ do you agree that the Pt. has been adequately resuscitated? If the answer is yes, end of active resuscitation has occurred. If the answer is no, end of active resuscitation has not occurred and you will need to ask prior to departure from the OR and/or IR suite.

Section 6.5.2 Rebleeding after Protocol Stop

If the situation occurs where the subject will require more products once the PROPPR protocol has been stopped because hemostasis has been achieved:

- Additional blood products can be given based on institutional guidelines, lab results and clinical guidance.
- The additional products will be documented on the case report form.
- The additional products will not be included in the ratio of products for study product analysis

Section 6.5.3 CRF Form #7: End of Resuscitation/PROPPR Protocol Treatment Form

General Instructions for completing CRF Form #7:

Complete this form for all randomized subjects. Use this form to document the end of resuscitation. If no randomized blood products were given, regardless of the reason, check the box at the top of CRF 7 and stop, the form is complete.

Question #1: Indicate the source of bleeding requiring the transfusion, select all that apply.
Source Documents: Hospital medical record, direct observation and data entry into the CRF.

Question #2: Record the PROPPR MT protocol stop date and time in dd/mmm/yy and hh:mm formats. The stop time for questions # 2 and # 3.b may be the same if the decision to stop the protocol was because the subject was adequately resuscitated.
Source Documents: Direct observation and data entry into the CRF.

Question #3: Indicate why the protocol was stopped and the stop time if indicated.

Anatomic hemostasis is defined as an objective assessment by the surgeon indicating bleeding within the surgical field has stopped and no further surgical interventions to control bleeding are anticipated. In the IR suite, ***anatomic hemostasis*** is defined as achieving resolution of blush after embolization.

Active Resuscitation stops after anatomic hemorrhage control based on the criteria above, and when the Surgeon and/or Anesthesiologists agree the subject is adequately resuscitated, based on the following criteria, if available:

a. Stable or increasing blood pressure, or
b. Stable or decreasing heart rate, or
c. Stable or increasing urine output, or
d. Decreasing drug requirements to maintain a stable blood pressure

Additional anatomic hemostasis times can be recorded should bleeding reoccur ***before*** active resuscitation end time has been called by checking the box for additional stop times and recording the information on form # 22. The time listed for end of active resuscitation should be the same time listed in question #2.

If further transfusions were deemed futile and/or subject expired, please document death on CRF 18 and notify the HDCC via email to PROPPR@uth.tmc.edu. Please include date and time of death and indicate if transfusion related. See Sections 12.6-12.7 for more information.

Follow the instructions below in situations where further transfusions were deemed futile and life support was maintained for organ donation:

1. The end of resuscitation stop date and time (question 2) is the time point when further transfusions were deemed futile.
2. Continue to collect post resuscitation blood products and research blood samples.
3. Stop all data collection at the time point when the subject is declared brain dead, even if maintained on life support for a longer period of time for organ donation.

If the protocol was stopped early per a request from the treating physician, RAs/Coordinators need to notify PI immediately. Document name of physician and reason for stopping, if applicable following notification of PI.

If the PROPPR MT protocol was stopped early or for "other" reasons, provide an explanation in the space provided or on form # 22.

Source Documents: Hospital medical record or direct observation and data entry into the CRF.

Question #4: Indicate if the blood bank was notified to stop the PROPPR protocol, recording the date and time in dd/mmm/yy and hh:mm formats.
Source Documents: Direct observation and data entry into the CRF.

Question #5: Record the subject's location at the time the PROPPR protocol was stopped.
If 'other" is selected, record the information on form # 22.
Source Documents: Direct observation and data entry into the CRF.

Question #6: Indicate if the subject had an unstable pelvic fracture by manual compression or testing. Data collection may require later follow-up if the end of resuscitation occurred early in the hospitalization before diagnostic test results were available. If 'yes" is selected, record the discovery date and time in dd/mmm/yy and hh:mm formats.
Source Documents: Hospital radiology and/or medical records.

Question #7: Indicate if the subject had an open femur fracture. If 'yes" is selected, record the discovery date and time in dd/mmm/yy and hh:mm formats.
Source Documents: Hospital radiology and/or medical records.

Use the following codes for unknown data values:
NR= Not Recorded/Not Done NA= Not Applicable NK= Unknown

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Study ID # ___ ___ ___ ___ ___ ___ ___ (Bar Code)

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CRF Version Date: 2013 MAR 01 Completed By: ___ ___ ___

Form 7: End of Resuscitation / PROPPR Protocol Treatment

Check here ☐ if no randomized blood products were given. *(i.e. the subject improved or died.)*

1. Source of bleeding requiring the transfusion: *(Select all that apply)*

☐ Abdomen ☐ Chest ☐ Intracranial ☐ Limb/Extremity ☐ Neck

☐ Pelvis ☐ Scalp/Face ☐ Not Noted/Unknown

2. PROPPR MT protocol stop date: __ __/__ __ __/__ __ Time: _____:_____
(dd/mmm/yy) *(24hr Clock in hh:mm)*

3. Why was the PROPPR MT protocol stopped? *(Select one)*

☐ Trauma Attending and/or Anesthesiologist determined subject was no longer bleeding, and adequately resuscitated.

a. Anatomic Hemostasis Time: **_____:_____** ☐ Actual ☐ Estimate
(24hr Clock in hh:mm)

Check here ☐ to report additional hemostasis times, document information on form #22.

b. Active Resuscitation with
Blood Products Stop Time: **_____:_____** ☐ Actual ☐ Estimate
(24hr Clock in hh:mm,)

☐ Further transfusions were deemed futile and/or subject expired.
(Document death on CRF #18 and notify HDCC)

☐ Unable to achieve hemostasis.

☐ Early protocol stop per treating physician request. *(*RA's/Coordinators are required to notify Site PI*)*
Physician Name: _____ Reason: _____

☐ Randomized blood products became unavailable.

☐ Other, (specify): _____

4. Was the Blood Bank notified to stop PROPPR MT protocol?

☐ Yes ↓ ☐ No ☐ Not Noted/Unknown
Date: __ __/__ __ __/__ __, Time: _____:_____
(dd/mmm/yy) *(24hr Clock in hh:mm)*

5. Location of subject at the end of resuscitation period: *(Select one)*

☐ ED ☐ OR ☐ IR ☐ ICU ☐ Intermediate Level Care

☐ Nursing Unit ☐ Other, specify: _____

6. Did the subject have an unstable pelvic fracture by manual compression? ☐ Yes ↓ ☐ No ☐ Not Noted/Unknown
Discovered on:
Date: __ __/__ __ __/__ __ Time: _____:_____
(dd/mmm/yy) *(24hr Clock in hh:mm)*

7. Did the subject have an open femur fracture? ☐ Yes ↓ ☐ No ☐ Not Noted/Unknown
Discovered on:
Date: __ __/__ __ __/__ __ Time: _____:_____
(dd/mmm/yy *(24hr Clock in hh:mm)*

Section 6.6 Notification of the HDCC of a randomization

The research team will email the HDCC within 24 hours to indicate a patient has been randomized. The email contact information is proppr@uth.tmc.edu.

Section 6.7 Completion of Site Master Enrollment Log

The master enrollment log will be used by the clinical site to link study ID's with subject PHI. This log is for site use only and should never be forwarded to the HDCC. Study monitors may view the master subject log for auditing purposes.

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FOR CLINICAL SITE USE ONLY

PROPPR Subject Master Log

Study ID #	Name	Medical Record #	SSN	Address	Telephone #

Chapter 7 - In-Hospital Data Collection

Section 7.1 Direct Patient Observation Time Frame

The research staff will be available 24/7 to screen and follow subjects enrolled into PROPPR.

The research staff will do “direct observation” data collection through the entire initial resuscitation period up to at least the 12th hour (unless the initial resuscitation lasts longer than 12 hours).

Once hemostasis has been achieved and the study containers have been returned to the blood bank, the research staff will monitor the patient frequently during the first 24 hour period following ED arrival.

It is recommended that the staff check on the patient at least hourly to monitor blood products and fluids given as well as other clinical information.

Another suggestion is to review the subject’s medical record at time of each study blood draw timepoint to document any products/fluids given and events which have occurred since the last blood draw.

Section 7.2 Instructions for Completing CRF Form #5: Initial 24 Hour Vital Signs and GCS

Complete this form for all randomized subjects. Record vital signs and the GCS at each hospital location within the first 24 hours from ED admission. Print additional pages of the form if needed.

Use the following codes to record unknown/missing data values:
ND = Not Detectable NR = Not Recorded/Not Done NA = Not Applicable
NP = Not Palpable NK = Unknown

The initial vital signs and GCS score obtained after ED arrival are recorded on form #1 and should not be duplicated here. Only record ED associated vital signs and GCS scores for subjects returning to the ED from another area. A subject admitted to the ED and transferred to Interventional Radiology (IR), and then back to the ED before finally arriving in the Intensive Care Unit (ICU) would have 3 lines of data on this form, one set of data collected on arrival to IR, one set of data collected after returning to the ED, and the third set of data collected after arrival in the ICU.

Use the following location codes: 1= ED, 2= Operating Room (OR), 3= IR, 4- Intensive Care Unit (ICU), 5= Intermediate Level Care (IMU) 6= Nursing Unit, 7= Other. An Intermediate level care unit is defined as providing continuous patient monitoring, like a telemetry or ICU step-down unit. If "other" is selected, record the information on form # 22.

Enter the first available vital signs and Glasgow Coma Score (GCS) obtained at each new location. Select the unit of measure for temperature. Use the following key for GCS scoring. Record the total GCS if component scores are unavailable.

GCS Scoring Key

Eye Movement (E)		Verbal (V)		Motor (M)	
1	No Response	1	No Response / Intubated	1	No Response
2	To Pain	2	Incomprehensible Sounds	2	Extension *(Decerebrate)*
3	To Verbal Command	3	Inappropriate Words	3	Flexion – *(Decorticate)*
4	Spontaneous	4	Disoriented, Converses	4	Flexion – Withdrawals From Pain
		5	Oriented, Converses	5	Localizes Pain
				6	Obeys Commands Appropriately

Indicate if the patient had an advanced airway at the time the verbal GCS component was assessed. For the purpose of GCS, the verbal score should be "1" in the presence of an advanced airway. Advanced airway is defined here as a device used as a method to assist and/or control ventilation. These devices mechanically prohibit verbal response testing. Devices used to assist and/or control ventilation are: bag value mask, oral ET, nasal ET, Combitube, LMA, King Airway, and cricothyrotomy/tracheostomy.

Indicate if the patient was chemically paralyzed at the time of the assessment. Paralytic drugs are defined as Pancuronium Bromide, Rocuronium, Succinylcholine, or Vercuronium.

Source Documents: Hospital medical records or direct observation and data entry into the CRF.

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Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012JUL25 Completed By: ___ ___ ___

Form 5: Initial 24hr Vital Signs & Glasgow Coma Scale (GCS)

(Record initial vital signs & GCS at ***each location*** *or change of location during the first 24 hrs. of hospitalization. Print additional pages if needed.)*

Location (LOCAT) Codes	
1	Emergency Department
2	Operating Room
3	Interventional Radiology
4	ICU
5	Intermediate Level Care
6	Nursing Unit
7	Other *(Specify)*

GCS Scoring Key

Component	Score	Description
Eye Movement (E)	1	No Response
	2	To Pain
	3	To Verbal Command
	4	Spontaneous
Verbal (V)	1	No Response / Intubated
	2	Incomprehensible Sounds
	3	Inappropriate Words
	4	Disoriented, Converses
	5	Oriented, Converses
Motor (M)	1	No Response
	2	Extension *(Decerebrate)*
	3	Flexion – *(Decorticate)*
	4	Flexion – Withdrawals From Pain
	5	Localizes Pain
	6	Obeys Commands Appropriately

** Initial ED arrival vitals and GCS are recorded on Form 1. Record only vitals and GCS associated with transfer **BACK** to the ED.**

LOCAT Code	Date *(dd/mmm/yy)*	Time *(hh:mm)*	Blood Pressure *(mmHg)*		Pulse *(beats/min)*	Temperature	Advanced Airway ?	Chemically Paralyzed?	Respiratory Rate	GCS Record EVM Scores OR GCS Total Score
			Systolic	Diastolic						
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___
	/ /	:	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___.___ □ F □ C	□ Yes □ No □ Unknown	□ Yes □ No □ Unknown	___ ___	E: ___ or GCS V: ___ Total:____ M: ___

Section 7.3 Instructions for Completing CRF Form # 6: IV Fluids and Blood Products

Use Form 6 to record IV fluids and blood products on randomized subjects. All IV fluids and blood products should be recorded from ED arrival through the first 24 hours of admission. Continue using Form 6 to record blood products administered after the first 24 hours through day 30 of the hospitalization. We are **not** collecting information on IV fluids administered after the first 24 hours of hospitalization.

Example: After ED admission and on OR visit, a subject spends 12 days in the ICU before being transferred to a nursing unit. All IV fluids and blood products given within the first 24 hours would be recorded on Form #6. On hospital day #16 the subject returns to the OR for a scheduled wound debridement and after a short stay in PACU, returns to the nursing unit. The following morning, on hospital day #17 the subject receives 2 units of RBC's. The 2 units of RBC's should be recorded on Form #6.

The IV fluid and blood product ***estimates*** listed on form #1 (amounts given from ED arrival to the 1st research blood sample collection) should be recorded here in detail.

Crystalloids vs. Colloids

Crystalloids are fluids that contain a combination of water and electrolytes. Common examples are NS, LR, D5W, D51/2 NS, D5 ¼, NS and Plasmalyte. Crystalloid solutions closely mimic the body's extra cellular fluid. Given I.V., crystalloid solutions diffuse through the capillary walls that separate plasma from interstitial fluid. They can be used to expand both intravascular and extra vascular fluid volume.

Colloids are fluids that contain dissolved particles, such as protein, sugar, and starch molecules, which are too big to pass through capillary walls. A colloid solution draws fluid from the interstitial and intracellular spaces, increasing intravascular volume. The degree of osmotic pull that a colloid exerts depends on its particle concentration. Albumin and Hetastarch are examples of colloid solutions.

Use the codes provided to identify the subject location and IV Fluids/blood products that were given. If the code for "other" is selected, record the information on form # 22. Record the start date and time in dd/mmm/yy and hh:mm formats. For IV fluids and blood products, "start" is defined as when the fluid bag was connected to IV tubing, or "spiked". Indicate the unit of measure; mLs for fluids and units for all blood products including cryoprecipitate. For IV fluids given at a very slow rate (i.e. IV drip), record the time the bag was spiked and the total amount given within the first 24 hours. Using the codes provided, indicate if the data was collected by direct observation or medical record review. For some blood product data elements (based on site specific blood bank labeling procedures) a later, additional medical record review may be required. Refer to the glossary at the end of this document for complete IV fluid and blood product definitions.

Record one blood product per CRF line. If the exact unit or accession number is unknown for the unit, a reasonable attempt should be made to match accession numbers by blood product type. Recording blood product unit or accession numbers are essential in tracking suspected transfusion reactions and will also prevent duplicate line entries in the database. The only exception to recording a unit or accession number is for cell save blood products that are collected, processed and immediately transfused back into patients.

In the last column on form #6, indicate the study time point associated with the blood product. Pre-randomization refers to IV fluids or blood products given from ED arrival up to the time point associated with breaking the blood transport container seal. If the subject did not receive any blood products pre-admission; that would have been recorded on form #3, then at least one unit of blood products should recorded as "pre-randomization" on form #6. For randomized blood products, indicate if the unit is the last "PROPPR MT" unit, i.e. end of active resuscitation. Select "post-randomization" for blood products given after the PROPPR MT protocol was stopped.

It's anticipated that some data lines will be recorded out of order on form #6. When entered into OpenClinica, the IV fluids and blood products will sort in order based on the start date and time. The source documents for form #6 will be the subject's medical records and associated blood bank records.

An *intentional* deviation from the assigned blood product administration ratio should be documented as a protocol deviation on form # 22.

Use the following codes for unknown data values:
NR= Not Recorded/Not Done NA= Not Applicable NK= Unknown

Print additional pages of the form if needed.

Excel Spreadsheet Procedures

1. Form 6 data can be recorded on an Excel spreadsheet provided by the HDCC or directly entered into OpenClinica. One option must be selected; either direct data entry into OpenCiinica or data upload using the spreadsheet. Spreadsheets submitted to the HDCC after form 6 data has been directly entered by the site Will NOT be accepted.
2. Record only one blood product per CRF line.
3. The blood product unit or accession number is a required data field. If the exact unit or accession number is unknown for the unit, a reasonable attempt should be made to match accession numbers by blood product type. Recording blood product unit or accession numbers are essential in tracking suspected transfusion reactions and will also prevent duplicate line entries in the database. The only exception for NOT recording a unit or accession number will be for cell saver blood products that are collected, processed and immediately transfused back into patients.
4. Always start with a blank spreadsheet, do not delete the cell contents or type over existing form data from another subject. Deleting cell contents will erase the value checks built into the form.
5. Indicate if the spreadsheet is for the initial resuscitation/24hrs or for 24hrs through day 30/discharge.
6. Don't submit the spreadsheet until you have all the data for the time period.
7. Do not modify the spreadsheet in any way.
8. Send the completed spreadsheet by e-mail to: proppr@uth.tmc.edu with the following in the e-mail message line: Form 6, Study ID # # # # # # #.
9. The data will appear as "saved complete" after the upload to OpenCiinica.
10. Once uploaded, data corrections, deletions, and/or additions must be made using the flag process. Please refer to the PROPPR eCRF training reference of Oct. 4th, 2012 on the PROPPR SharePoint website, Training & Resources Folder/ e-CRF subfolder. Procedures for data entry.

FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: _____ **Check One:** ◉ Initial Resuscitation to 24hrs ○ 24hrs to 30 Day/Discharge

Location Code		Blood Products					
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)		
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)		
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)		
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)		
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)		
6	Nursing Unit	6	Platelets Apheresis (Plt - A)				
7	Other - (specify)						

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date: dd/mmm/yy	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date: dd/mmm/yy	Product given at what time point (1-4)	CRF Completed By: (Initials)

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 20 12FEB04)

Study Subject ID:	

Location Code		IV Fluid Code			
		Colloids		Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

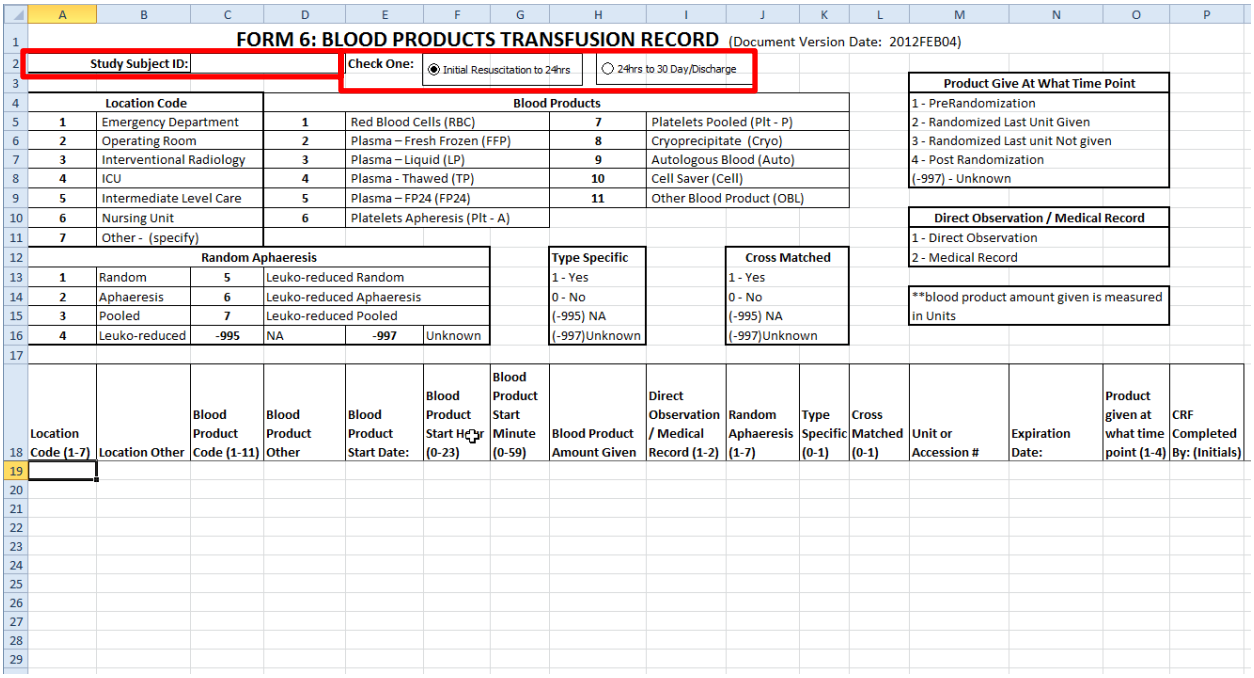
Direct Observation / Medical Record
1 - Direct Observation 2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date dd/mmm/yy	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

PROPPR Form – 6 Transfusion Record

Excel Template Instructions:



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

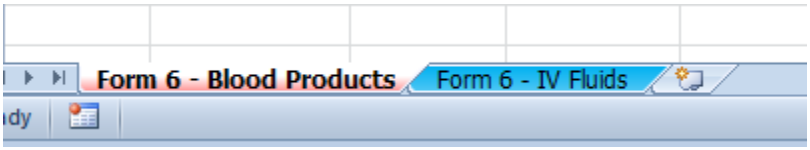
**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Before starting data entry, enter the Subject ID and select which form is being completed:

- Initial Resuscitation to 24hrs.
- 24hrs to 30 Day /Discharge

There are two worksheets:



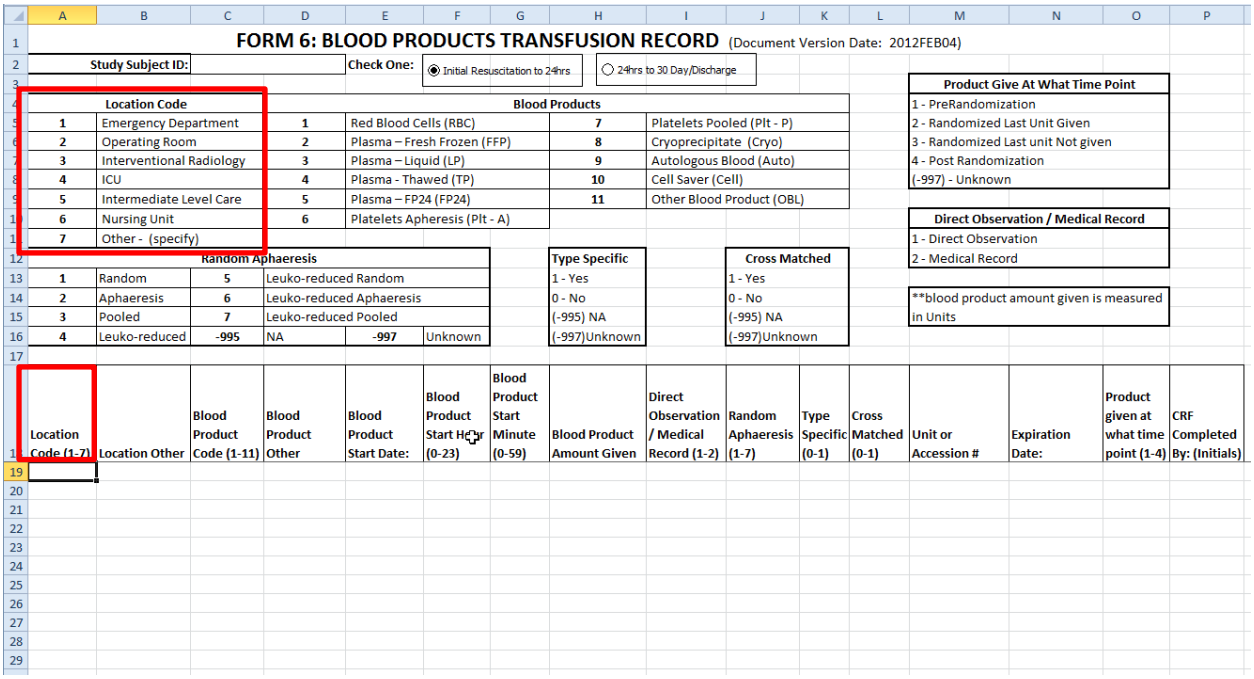
- Form 6 - Blood Products – red highlight
- Form 6 - IV Fluids – blue highlight

You can switch between these worksheets by clicking once on the highlighted tab.

Form 6 - Blood Products Worksheet

There are up to sixteen items to complete per record.

1. Location Code



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

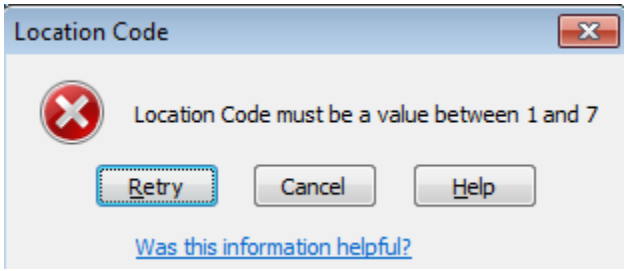
Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

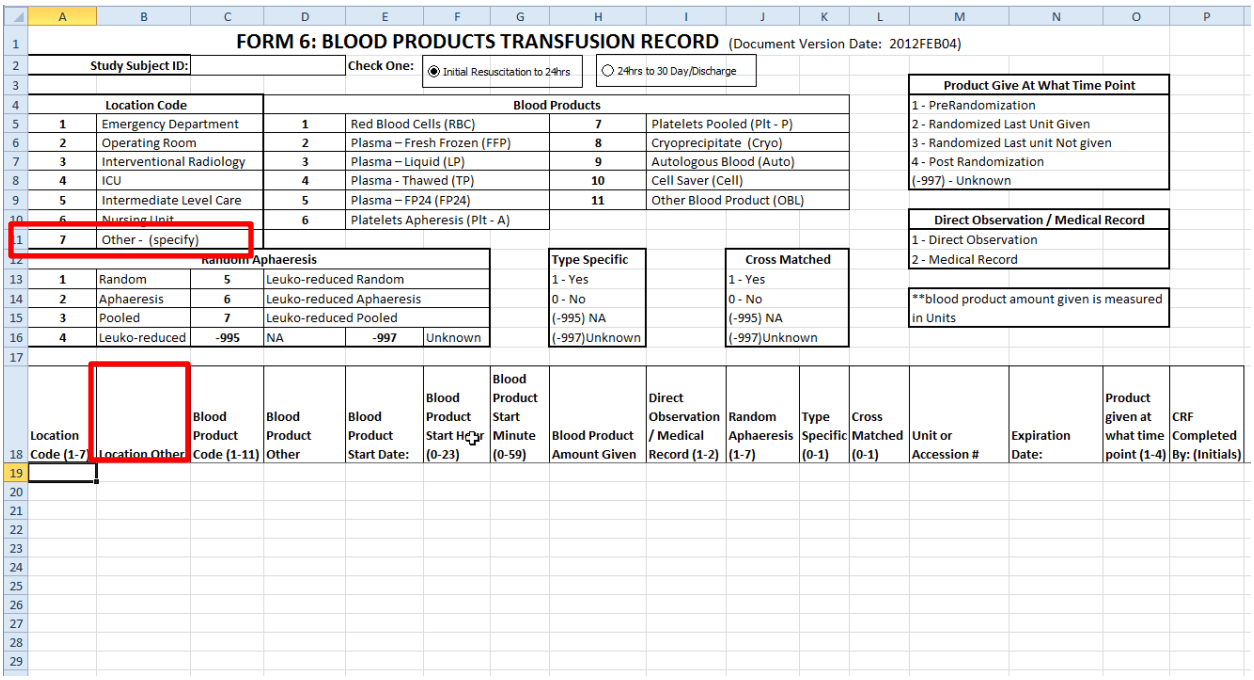
The location code can have a numeric value of 1-7, no other value is allowed.



Entering a value outside the range of 1-7, will open an error message:

- Click Retry to remove the current entry and reenter the value in the range 1-7
- Click Cancel to remove the current entry
- Click Help

2. Location Other



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

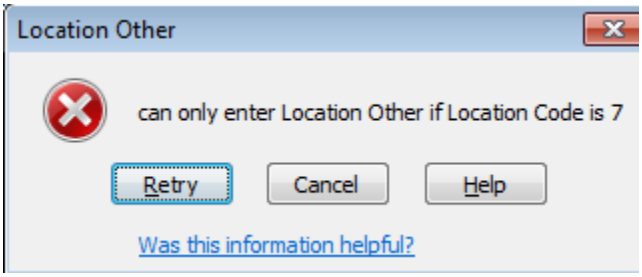
Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Location Other can only be filled out when Location Code has the value of '7'. The Location Other allows text to be entered describing the location that is not listed in the Location Codes.

Entering a value when the Location Code contains a value other than 7 will popup an error message:



- Click Cancel to remove the current entry

3. Blood Product Code

FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

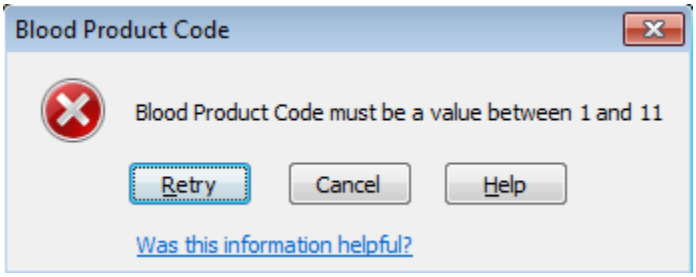
Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

The Blood Product Code can have a numeric value of 1-11, no other value is allowed.



Entering a value outside the range of 1-11, will open an error message:

- Click Retry to remove the current entry and reenter the value in the range 1-11
- Click Cancel to remove the current entry
- Click Help

4. Blood Product Other

FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

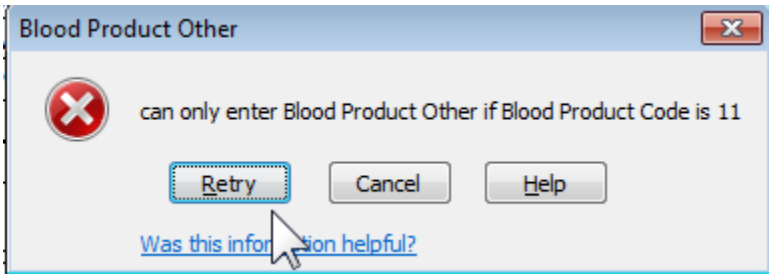
Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

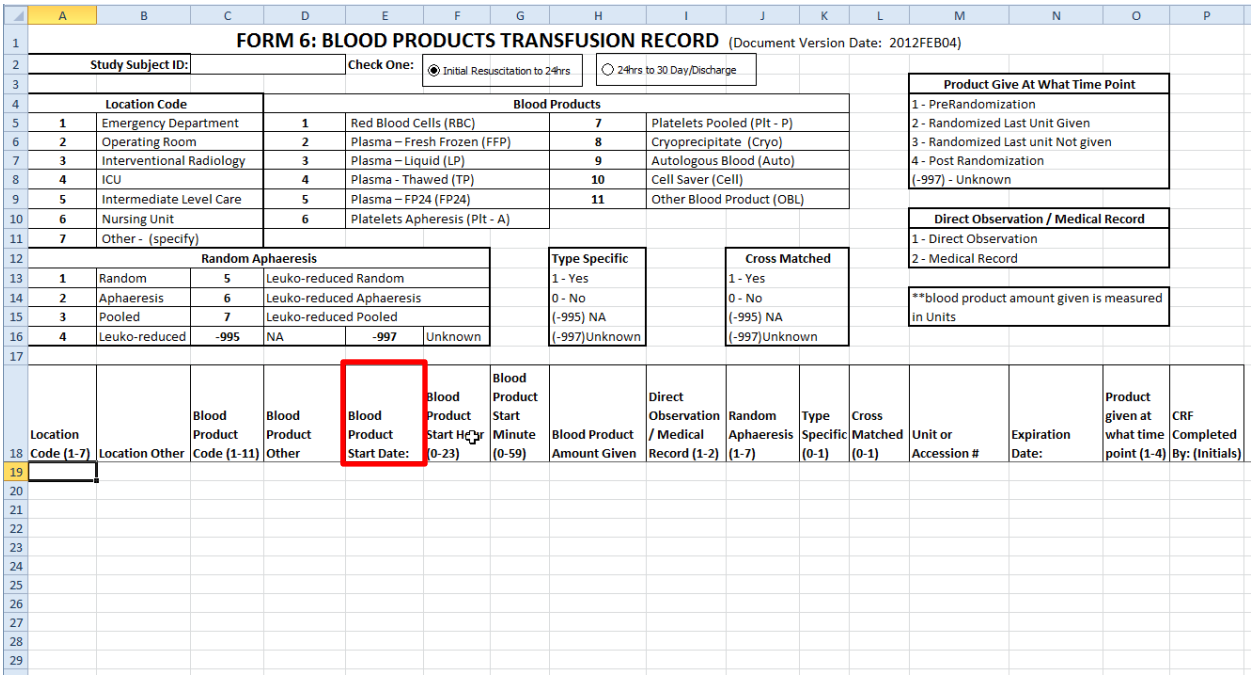
Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Blood Product Other can only be entered if the Blood Product Code is 11. Blood Product Other allows text to describe a Blood Product that is not listed in the Blood Product Codes. Entering data when the Blood Product Code is any value other than 11, will open a popup error message.



- Click Cancel to remove the current entry

5. Blood Product Start Date



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | **Check One:** ◉ Initial Resuscitation to 24hrs | ○ 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

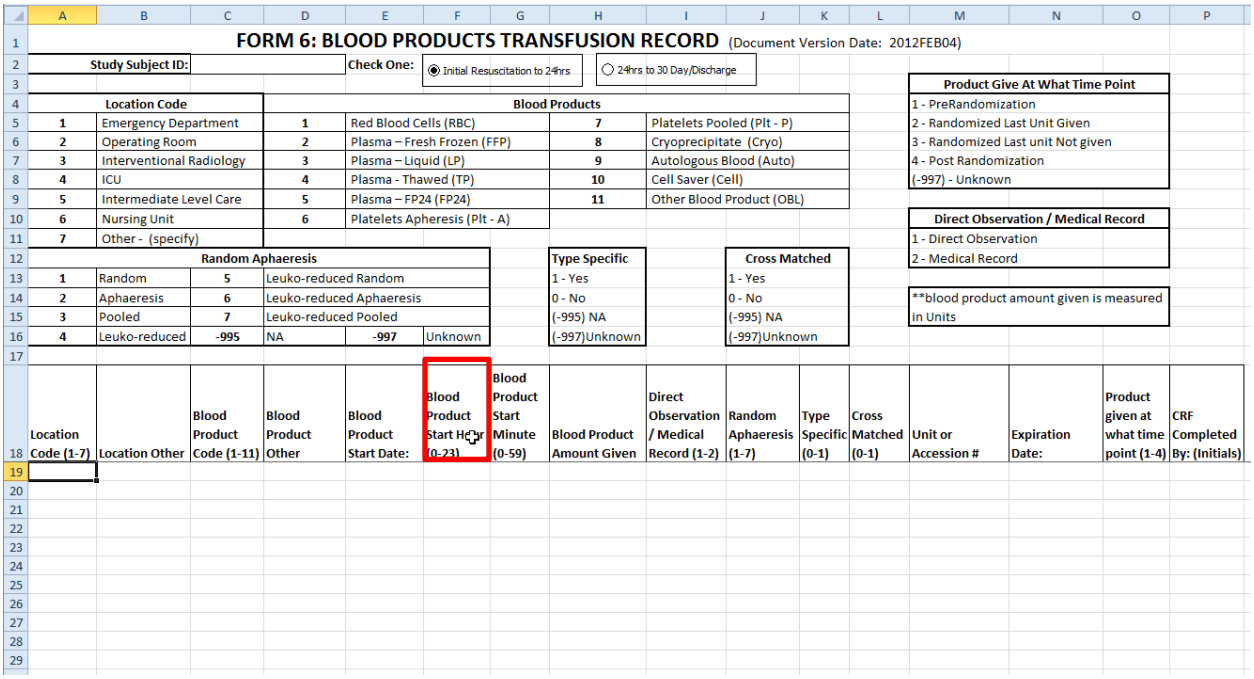
**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

The Blood Product Start Date must be in the following format: dd-mmm-yyyy

Entering a date will automatically be formatted to dd-mmm-yyyy format.

6. Blood Product Start Hour



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Blood Product Start Hour can be a numeric value between 0 and 23, it can also have the following codes:

-995 for Not Applicable

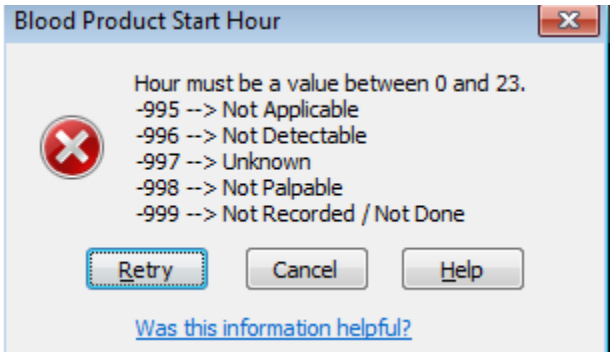
-996 for Not Detectable

-997 for Unknown

-998 for Not Palpable

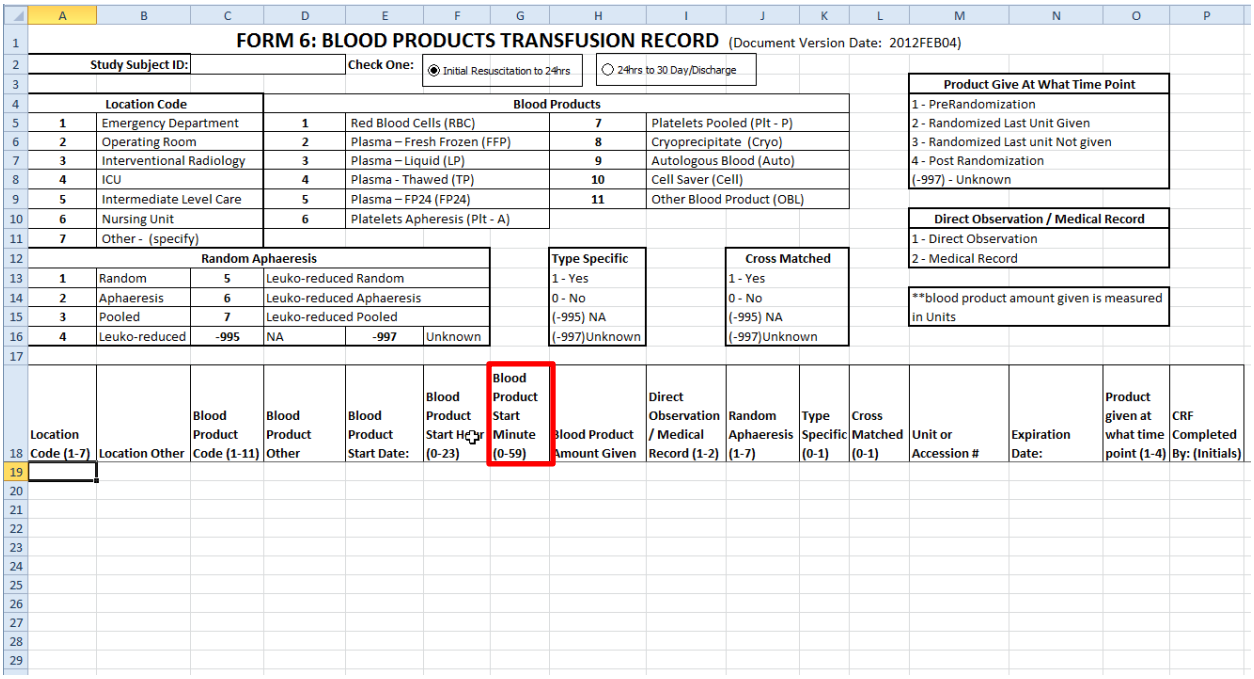
-999 for Not Recorded/Not Done

Entering a value other outside of the 0-23 or that is not one of the above listed codes will pop up an error message:



- Click Retry to remove the current entry and reenter the value in the range 0-23, or –XXX code
- Click Cancel to remove the current entry
- Click Help

7. Blood Product Start Minute



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Blood Product Start Minute can be a numeric value between 0 and 59, it can also have the following codes:

-995 for Not Applicable

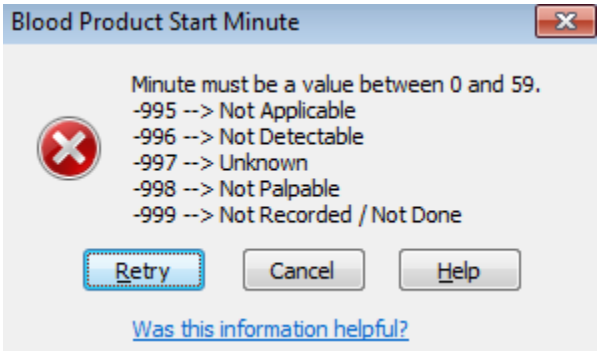
-996 for Not Detectable

-997 for Unknown

-998 for Not Palpable

-999 for Not Recorded/Not Done

Entering a value other outside of the 0-59 or that is not one of the above listed codes will pop up an error message:



- Click Retry to remove the current entry and reenter the value in the range 0-59, or –XXX code
- Click Cancel to remove the current entry
- Click Help

8. Blood Product Amount Given

FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Blood Product Amount Given can be certain values based upon the Blood Product Code:

If Blood Product Code is 10 – Cell Saver, the Blood Product Amount Given can be greater than 1

If Blood Product Code is 2 – Fresh Frozen Plasma(FFP), the Blood Product Amount Given can be 1 unit or 2 units.

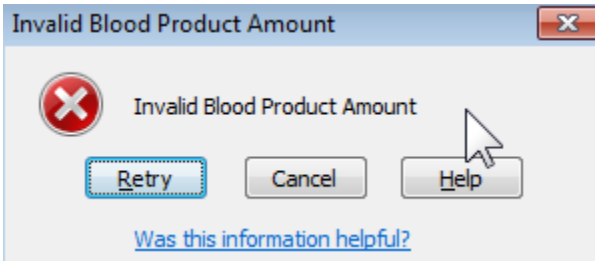
1 – 1 unit of Fresh Frozen Plasma (FFP)

2 – 1 unit of Jumbo Plasma

*entering a value that is greater than 2 will pop up an error message, when Blood Product Code is 2.

If Blood Product Code is 1,3,4,5,6,7,8, or 9, the Blood Product Amount Given can only be 1, representing one unit of Blood Product

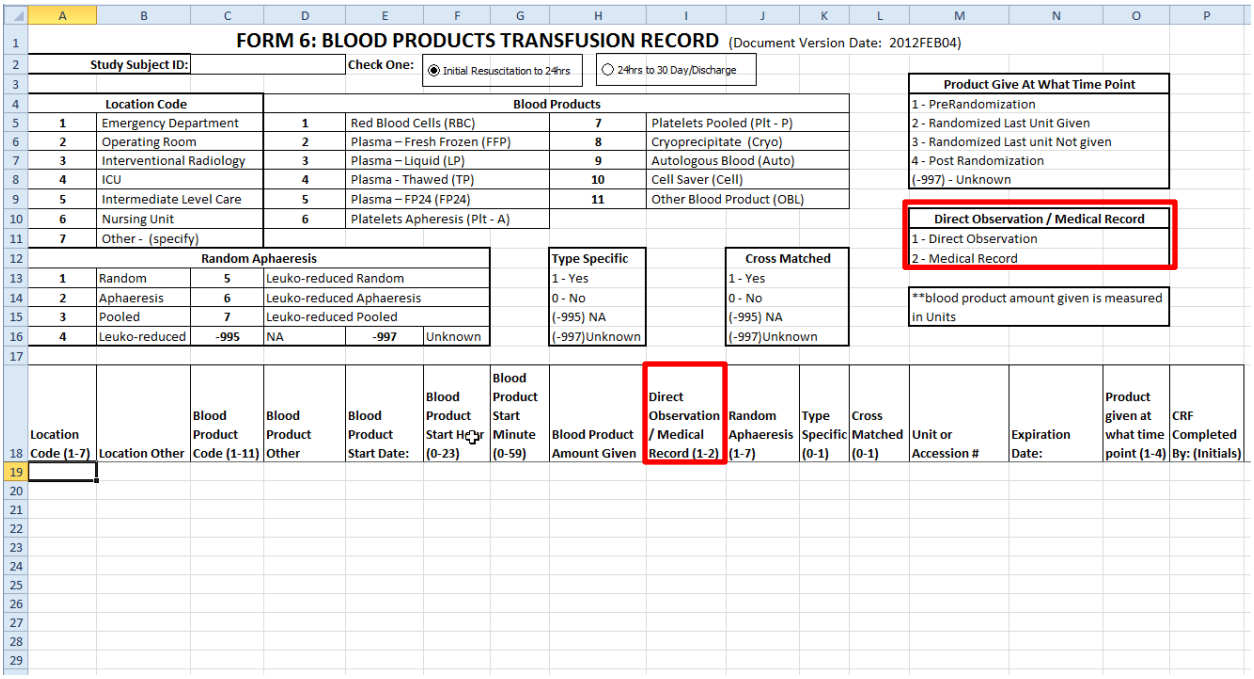
*entering a value other than 1, will pop up an error message, when Blood Product Code is 1,3,4,5,6,7,8, or 9



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

Form 6 Template Blood Product Worksheet -

9. Direct Observation / Medical Record



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

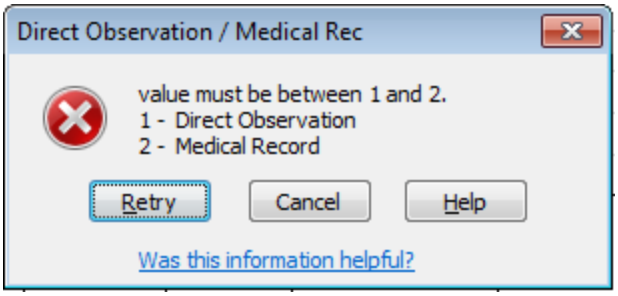
Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Direct Observation / Medical Record can be one of the following values:

1 – Direct Observation

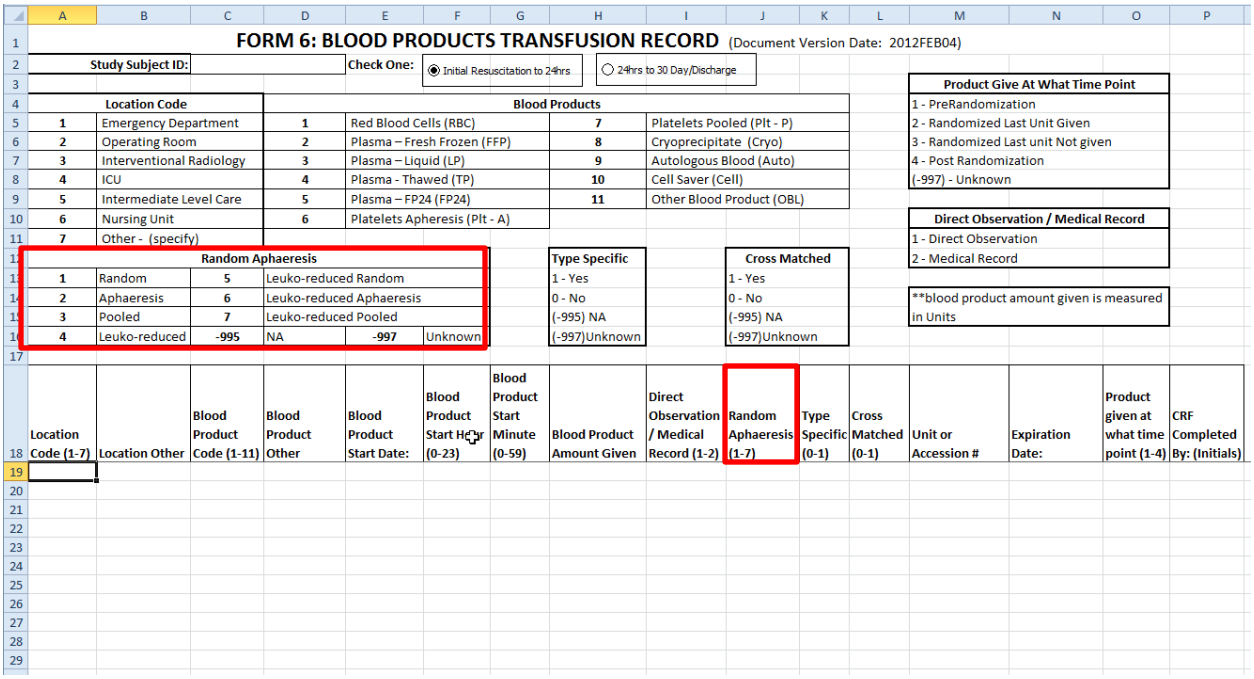
2 – Medical Record

Entering any other value will pop up an error message.



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

10. Random Aphaeresis



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

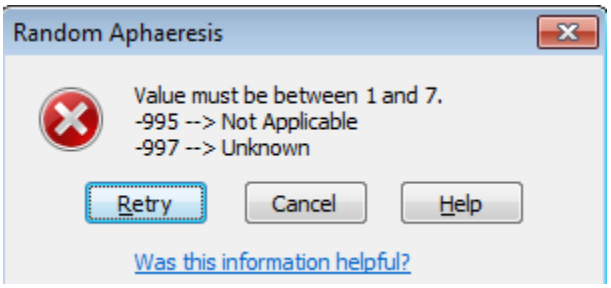
Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Random Aphaeresis can be a value between 1 and 7 or one of the following codes:

-995 for Not Applicable

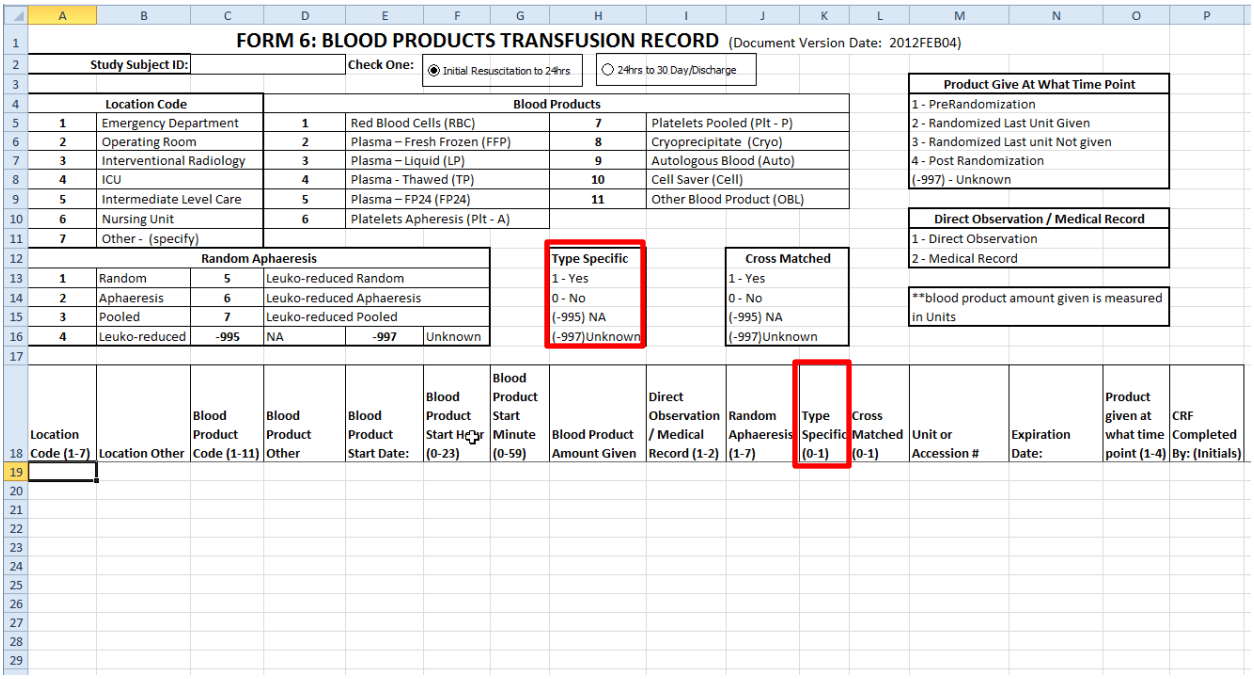
-997 for unknown

entering any other value will pop up an error message:



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

11. Type Specific



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Type Specific can be one of the following values:

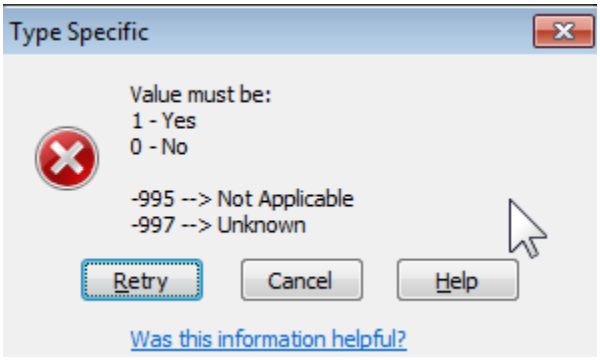
1 – Yes

2 – No

-995 – Not Applicable

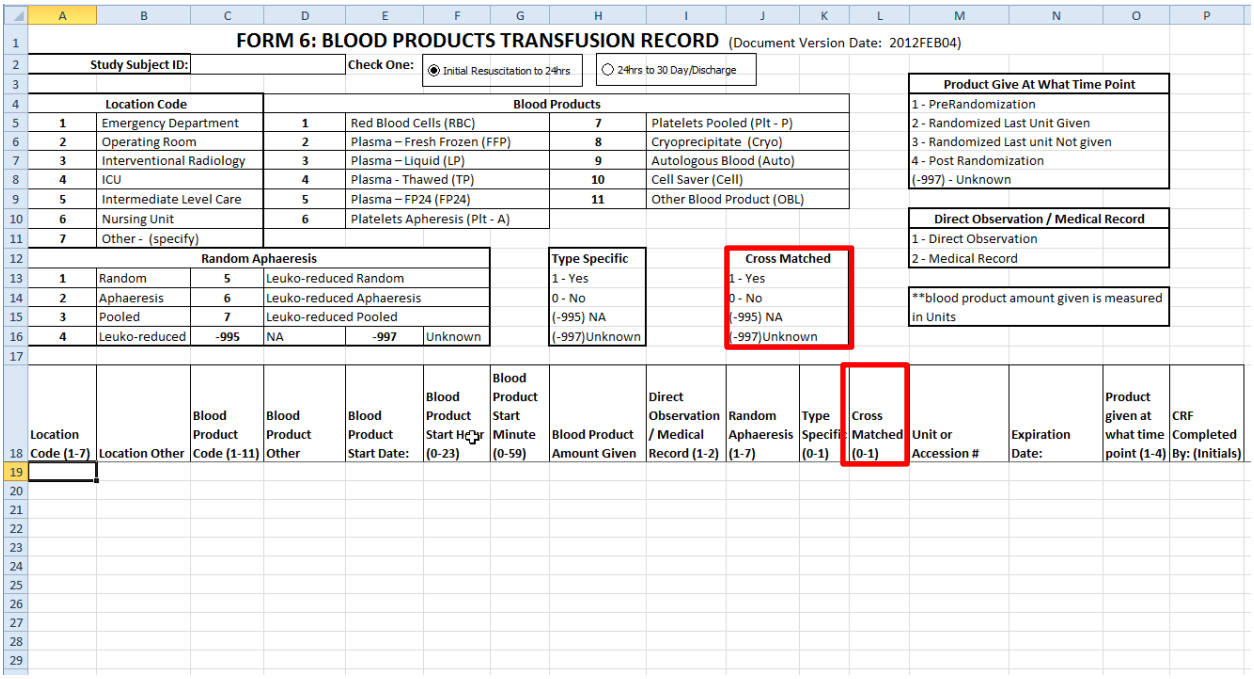
-997 – unknown

entering any other value will pop up an error message



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

12. Cross Matched



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Cross Matched can be one of the following values:

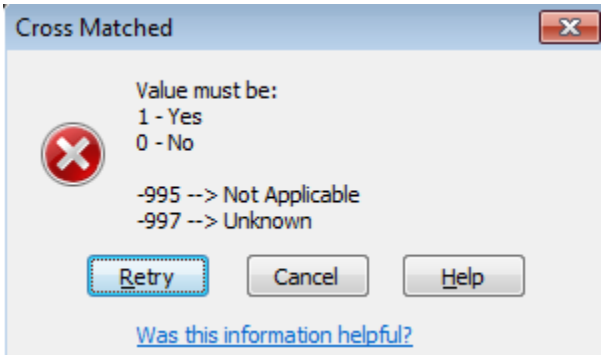
1 – Yes

2 – No

-995 – Not Applicable

-997 – unknown

entering any other value will pop up an error message



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

13. Unit or Accession Number

FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | **Check One:** (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

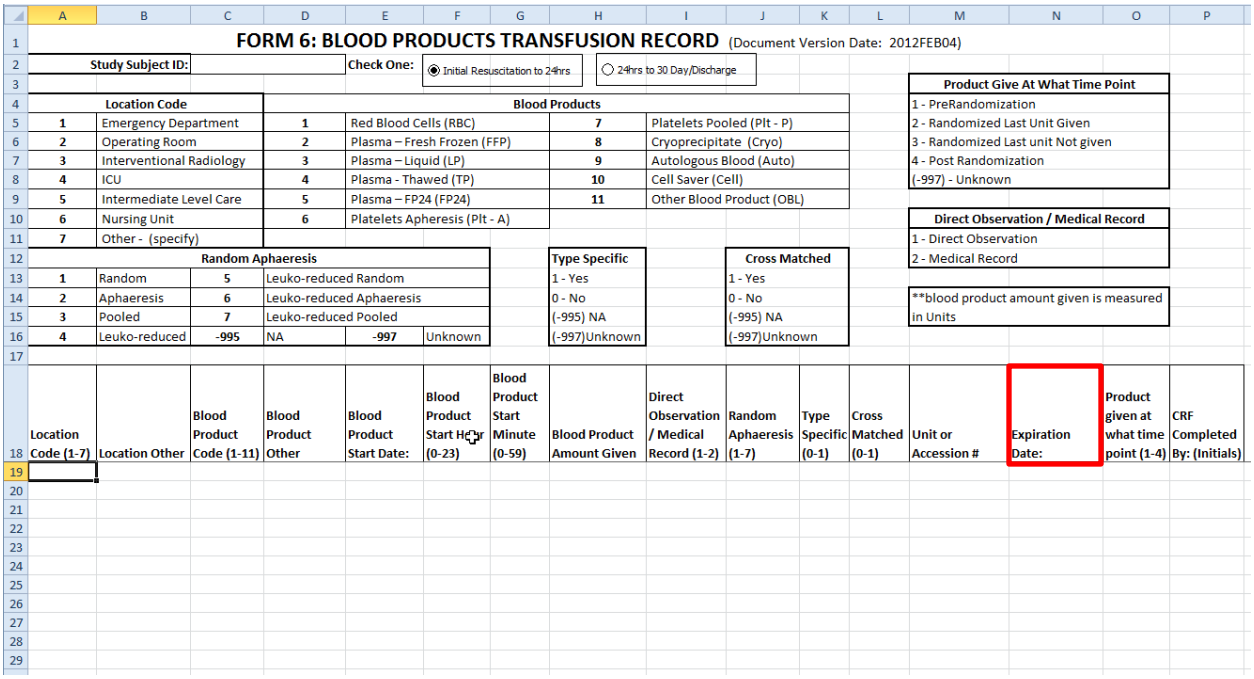
Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

ADD NOTES

14. Expiration Date



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

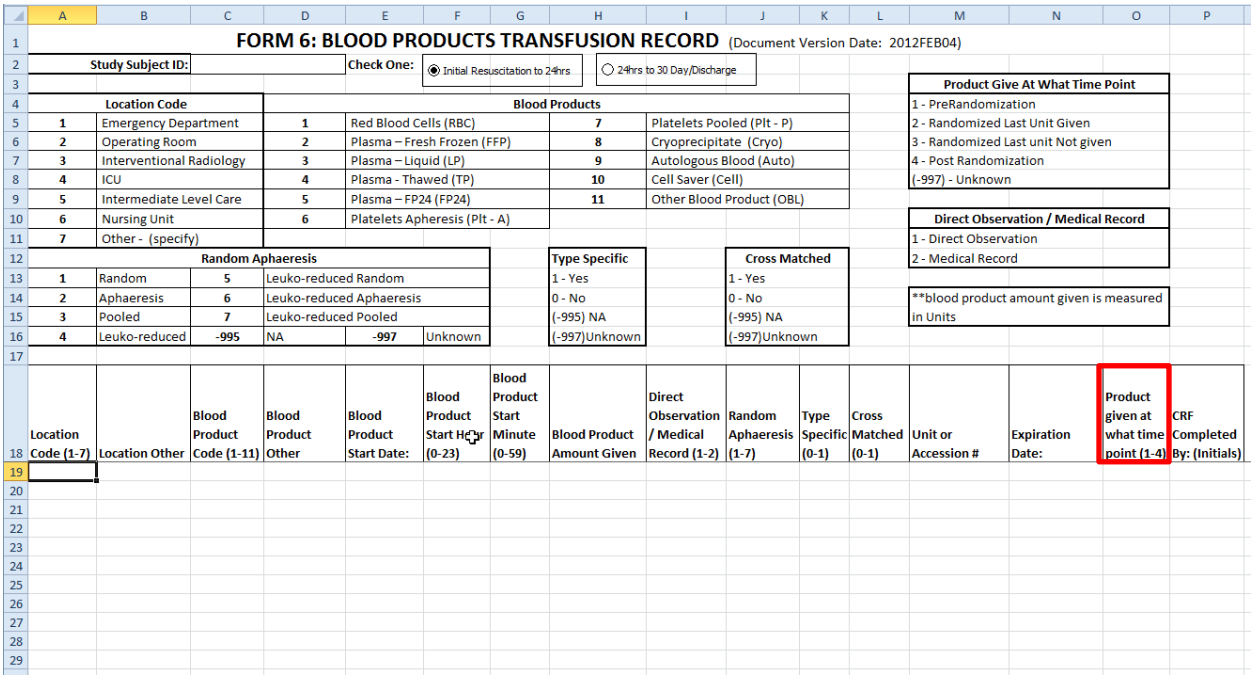
**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Expiration Date must be in the following format: dd-mmm-yyyy

Entering a date will automatically be formatted to dd-mmm-yyyy format.

15. Product given at what time point



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

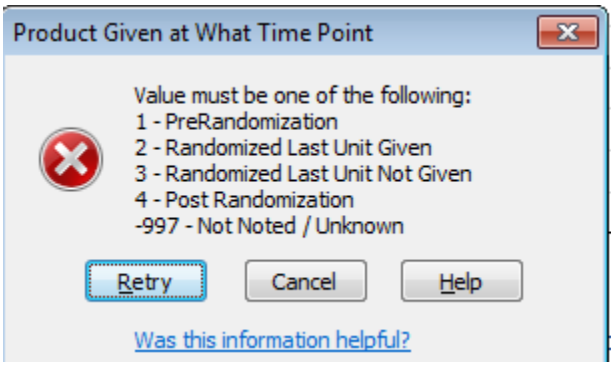
**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials)

Product given at what time point can be only be one of the following values:

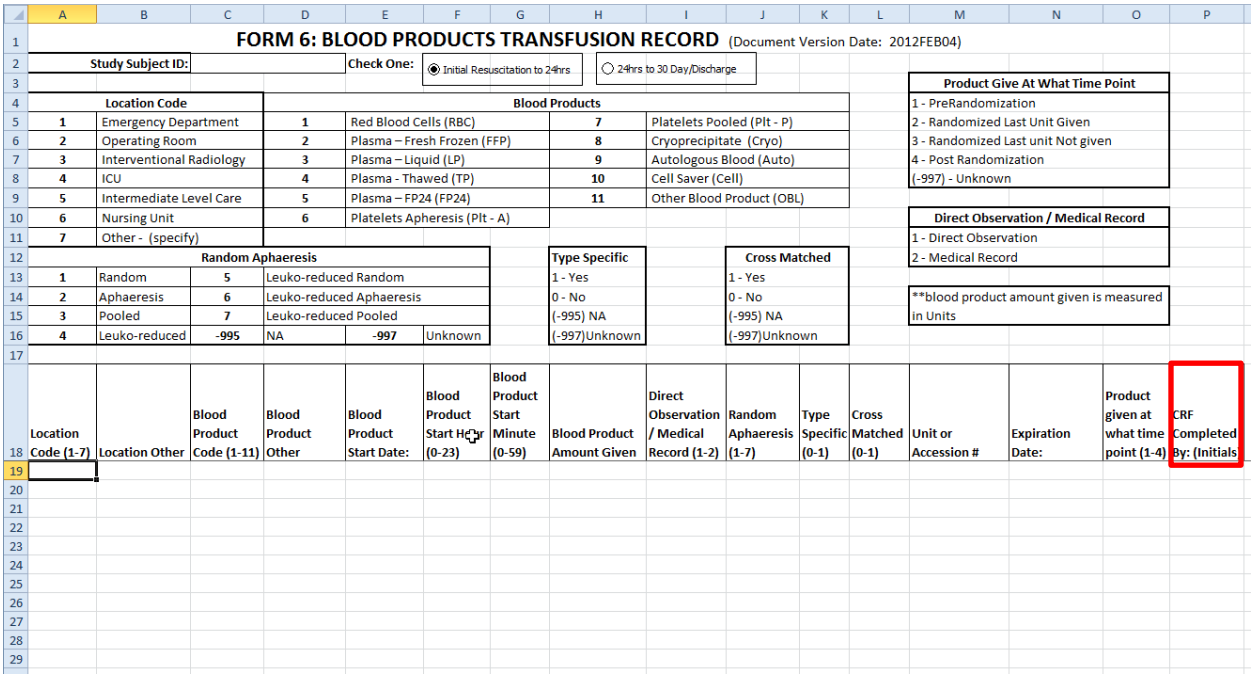
1 for PreRandomization
2 for Randomized Last Unit Given
3 for Randomized Last unit Not given
4 for Post Randomization
-997 for Unknown

Entering any other value will pop up an error message.



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

16. CRF Completed By



FORM 6: BLOOD PRODUCTS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID: | Check One: (•) Initial Resuscitation to 24hrs | ( ) 24hrs to 30 Day/Discharge

Location Code		Blood Products			
1	Emergency Department	1	Red Blood Cells (RBC)	7	Platelets Pooled (Plt - P)
2	Operating Room	2	Plasma – Fresh Frozen (FFP)	8	Cryoprecipitate (Cryo)
3	Interventional Radiology	3	Plasma – Liquid (LP)	9	Autologous Blood (Auto)
4	ICU	4	Plasma - Thawed (TP)	10	Cell Saver (Cell)
5	Intermediate Level Care	5	Plasma – FP24 (FP24)	11	Other Blood Product (OBL)
6	Nursing Unit	6	Platelets Apheresis (Plt - A)		
7	Other - (specify)				

Random Aphaeresis					
1	Random	5	Leuko-reduced Random		
2	Aphaeresis	6	Leuko-reduced Aphaeresis		
3	Pooled	7	Leuko-reduced Pooled		
4	Leuko-reduced	-995	NA	-997	Unknown

Type Specific
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Cross Matched
1 - Yes
0 - No
(-995) NA
(-997)Unknown

Product Give At What Time Point
1 - PreRandomization
2 - Randomized Last Unit Given
3 - Randomized Last unit Not given
4 - Post Randomization
(-997) - Unknown

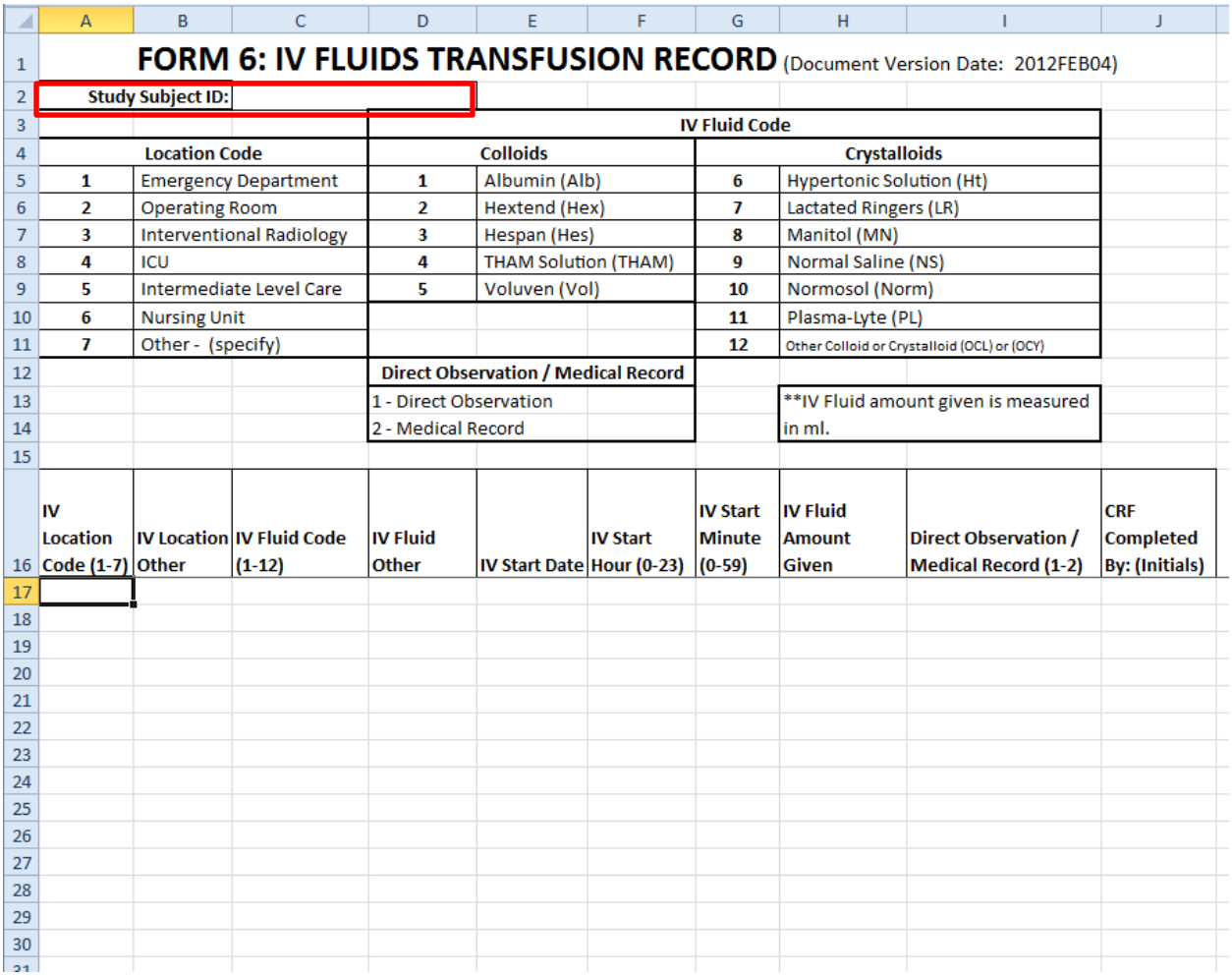
Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**blood product amount given is measured in Units

Location Code (1-7)	Location Other	Blood Product Code (1-11)	Blood Product Other	Blood Product Start Date:	Blood Product Start Hour (0-23)	Blood Product Start Minute (0-59)	Blood Product Amount Given	Direct Observation / Medical Record (1-2)	Random Aphaeresis (1-7)	Type Specific (0-1)	Cross Matched (0-1)	Unit or Accession #	Expiration Date:	Product given at what time point (1-4)	CRF Completed By: (Initials

CRF Completed By, enter the initials of the person that completed the CRF.

Form 6 – IV Fluids Worksheet



FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

IV Fluid Code

Location Code		Colloids		Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record

1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

Enter the Study Subject ID (must match the Study Subject ID from the Blood Products worksheet)

There are up to 10 items to complete for each IV Fluid record. Data entry begins on row 17.

1. IV Location Code

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

Location Code	
1	Emergency Department
2	Operating Room
3	Interventional Radiology
4	ICU
5	Intermediate Level Care
6	Nursing Unit
7	Other - (specify)

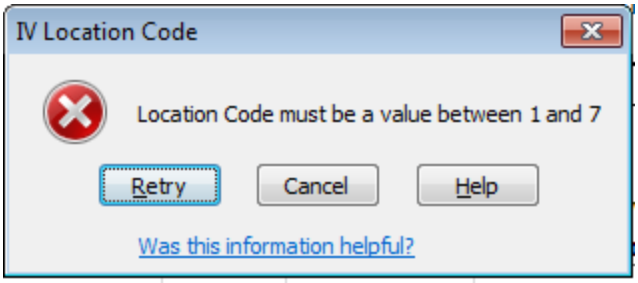
IV Fluid Code			
Colloids		Crystalloids	
1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Hespan (Hes)	8	Manitol (MN)
4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Voluven (Vol)	10	Normosol (Norm)
		11	Plasma-Lyte (PL)
		12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Location Code can be a value between 1 and 7, entering any other value will pop up an error message



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

2. IV Location Other

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

Location Code	
1	Emergency Department
2	Operating Room
3	Interventional Radiology
4	ICU
5	Intermediate Level Care
6	Nursing Unit
7	Other - (specify)

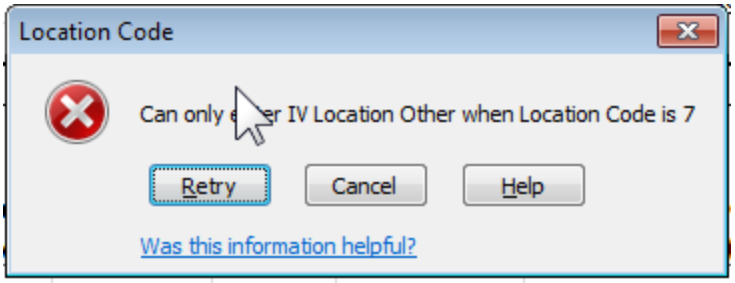
IV Fluid Code			
Colloids		Crystalloids	
1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Hespan (Hes)	8	Manitol (MN)
4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Voluven (Vol)	10	Normosol (Norm)
		11	Plasma-Lyte (PL)
		12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Location Other can only be filled out when the IV Location Code is 7, entering the IV Location Other when IV Location Code is any value other than 7, will pop up an error message.



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

3. IV Fluid Code

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

IV Fluid Code

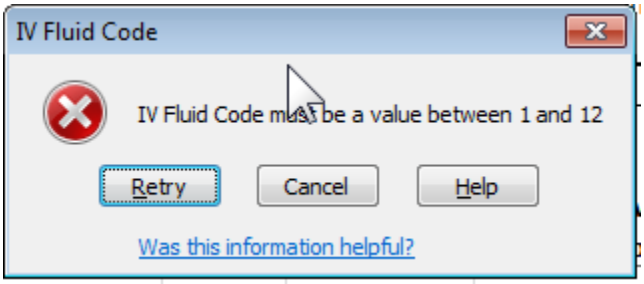
Location Code		Colloids		Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Fluid Code can be any value between 1 and 12, entering any other value will pop up an error message



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

Form 6 Template – IV Fluid Worksheet

4. IV Fluid Other

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

IV Fluid Code			
Location Code		Colloids	
1	Emergency Department	1	Albumin (Alb)
2	Operating Room	2	Hextend (Hex)
3	Interventional Radiology	3	Hespan (Hes)
4	ICU	4	THAM Solution (THAM)
5	Intermediate Level Care	5	Voluven (Vol)
6	Nursing Unit		
7	Other - (specify)		

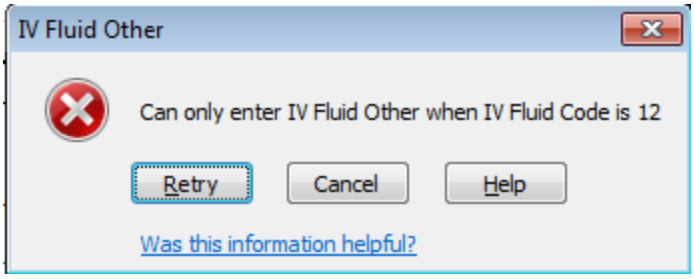
Crystalloids	
6	Hypertonic Solution (Ht)
7	Lactated Ringers (LR)
8	Manitol (MN)
9	Normal Saline (NS)
10	Normosol (Norm)
11	Plasma-Lyte (PL)
12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Fluid Other can only be filled out when IV Fluid Code is 12, entering IV Fluid Other when IV Fluid Code is any other value will pop up an error message.



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

5. IV Start Date

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

IV Fluid Code					
Location Code		**Colloids**		**Crystalloids**	
1	Emergency Department	**1**	Albumin (Alb)	**6**	Hypertonic Solution (Ht)
2	Operating Room	**2**	Hextend (Hex)	**7**	Lactated Ringers (LR)
3	Interventional Radiology	**3**	Hespan (Hes)	**8**	Manitol (MN)
4	ICU	**4**	THAM Solution (THAM)	**9**	Normal Saline (NS)
5	Intermediate Level Care	**5**	Voluven (Vol)	**10**	Normosol (Norm)
6	Nursing Unit			**11**	Plasma-Lyte (PL)
7	Other - (specify)			**12**	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record		**IV Fluid amount given is measured in ml.**
1	Direct Observation	
2	Medical Record	

IV Location Code (1-7)	**IV Location Other**	**IV Fluid Code (1-12)**	**IV Fluid Other**	**IV Start Date**	**IV Start Hour (0-23)**	**IV Start Minute (0-59)**	**IV Fluid Amount Given**	**Direct Observation / Medical Record (1-2)**	**CRF Completed By: (Initials)**

IV Start Date must be in the following format: dd-mmm-yyyy

Entering a date will automatically be formatted to dd-mmm-yyyy format.

6. IV Start Hour

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

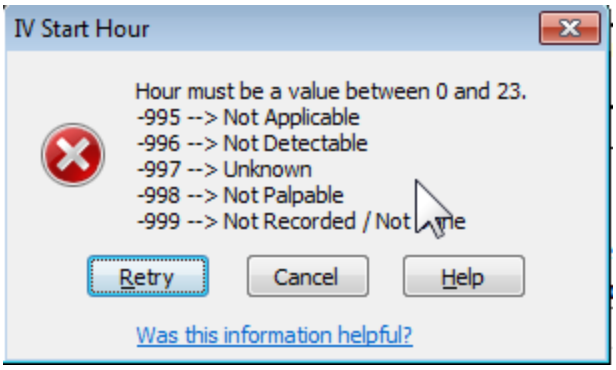
Location Code		IV Fluid Code: Colloids		IV Fluid Code: Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Start Hour can be a numeric value between 0 and 23, it can also have the following codes:
-995 for Not Applicable
-996 for Not Detectable
-997 for Unknown
-998 for Not Palpable
-999 for Not Recorded/Not Done
Entering a value other outside of the 0-23 or that is not one of the above listed codes will pop up an error message:



- Click Retry to remove the current entry and reenter the value in the range 0-23, or –XXX code
- Click Cancel to remove the current entry
- Click Help

Form 6 Template – IV Fluid Worksheet

7. IV Start Minute

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

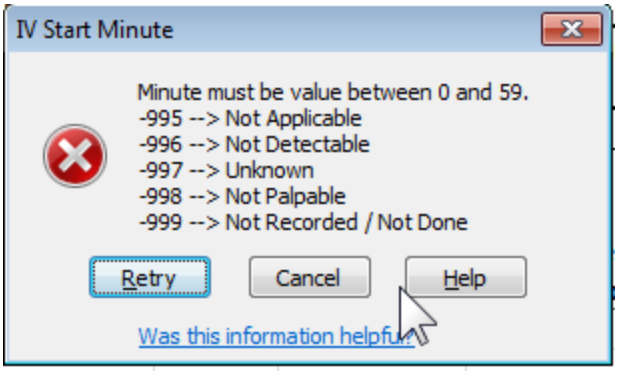
Location Code		IV Fluid Code: Colloids		IV Fluid Code: Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Start Minute can be a numeric value between 0 and 59, it can also have the following codes:
-995 for Not Applicable
-996 for Not Detectable
-997 for Unknown
-998 for Not Palpable
-999 for Not Recorded/Not Done
Entering a value other outside of the 0-59 or that is not one of the above listed codes will pop up an error message:



- Click Retry to remove the current entry and reenter the value in the range 0-59, or –XXX code
- Click Cancel to remove the current entry
- Click Help

Form 6 Template – IV Fluid Worksheet

8. IV Fluid Amount Given

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

Location Code		Colloids		Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record

1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

IV Fluid Amount Given is measured in ml. Can enter any numeric value.

Form 6 Template – IV Fluid Worksheet

9. Direct Observation / Medical Record

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

Location Code		IV Fluid Code: Colloids		IV Fluid Code: Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record
1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

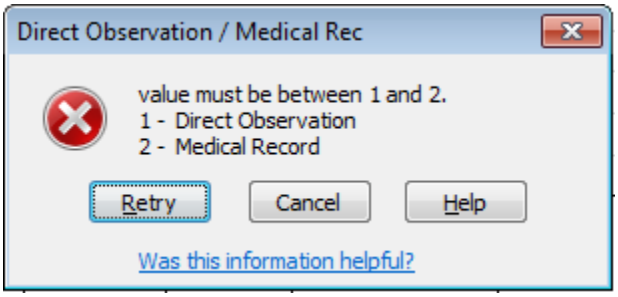
IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

Direct Observation / Medical Record can be one of the following values:

1 – Direct Observation

2 – Medical Record

Entering any other value will pop up an error message.



- Click Retry to remove the current entry and reenter the value
- Click Cancel to remove the current entry
- Click Help

Form 6 Template – IV Fluid Worksheet

10. CRF Completed By

FORM 6: IV FLUIDS TRANSFUSION RECORD (Document Version Date: 2012FEB04)

Study Subject ID:

Location Code		IV Fluid Code: Colloids		IV Fluid Code: Crystalloids	
1	Emergency Department	1	Albumin (Alb)	6	Hypertonic Solution (Ht)
2	Operating Room	2	Hextend (Hex)	7	Lactated Ringers (LR)
3	Interventional Radiology	3	Hespan (Hes)	8	Manitol (MN)
4	ICU	4	THAM Solution (THAM)	9	Normal Saline (NS)
5	Intermediate Level Care	5	Voluven (Vol)	10	Normosol (Norm)
6	Nursing Unit			11	Plasma-Lyte (PL)
7	Other - (specify)			12	Other Colloid or Crystalloid (OCL) or (OCY)

Direct Observation / Medical Record

1 - Direct Observation
2 - Medical Record

**IV Fluid amount given is measured in ml.

IV Location Code (1-7)	IV Location Other	IV Fluid Code (1-12)	IV Fluid Other	IV Start Date	IV Start Hour (0-23)	IV Start Minute (0-59)	IV Fluid Amount Given	Direct Observation / Medical Record (1-2)	CRF Completed By: (Initials)

CRF Completed By, enter the initials of the person that completed the CRF.

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CRF Version Date: 2012NOV15 Completed By: ___ ___ ___

Form 6: IV Fluids & Blood Products Transfusion Record

*(Record blood products in **units** and all other fluids in **mL.s** using the **codes** below. Print additional pages if needed.)*

Location (LOCAT) Codes	
1	Emergency Department
2	Operating Room
3	Interventional Radiology
4	ICU
5	Intermediate Level Care
6	Nursing Unit
7	Other: *(Specify)*

Blood Products Codes			
1	Red Blood Cells **(RBC)**	7	Platelets - Pooled **(Plt-P)**
2	Plasma – Fresh Frozen **(FFP)**	8	Cryoprecipitate - **(Cryo)**
3	Plasma – Liquid **(LP)**	9	Autologous Blood **(Auto)**
4	Plasma - Thawed **(TP)**	10	Cell Saver - **(Cell)**
5	Plasma – FP24 **(FP24)**	11	Other Blood Product **(OBL)**
6	Platelets - Apheresis **(Plt -A)**		

MR: Data Collected from Medical Record Review	**DO:** Direct Observation

Colloids Codes		Crystalloids Codes	
1	Albumin **(Alb)**	6	Hypertonic Solution **(Ht)**
2	Hextend **(Hex)**	7	Lactated Ringers **(LR)**
3	Hespan **(Hes)**	8	Manitol **(MN)**
4	THAM Solution (THAM)	9	Normal Saline **(NS)**
5	Voluven **(Vol)**	10	Normosol **(Norm)**
		11	Plasma-Lyte **(PL)**
12	**Other** Colloid **(OCL)** or Crystalloid **(OCY)**		

****Document any deviations from MT protocol on form #22. ****

Complete for All Blood Products & IV Fluids							**Complete for ONLY Blood Products**				
LOCAT Code	Blood / Fluid Code	Start Date *(dd/mmm/yy)*	Start Time *(hh:mm)*	Amount Given		DO MR	Random Aphaeresis	Type Specific	Cross-Matched	Unit or Accession #	Product Given At What Time Point?
		/ /	:	___ ___ ___ ___	☐ Units ☐ ml.	☐ DO ☐ MR	☐ Aphaeresis ☐ Leuko-reduced ☐ NA ☐ NK ☐ Pooled ☐ Random	☐ Yes ☐ No ☐ NA ☐ NK	☐ Yes ☐ No ☐ NA ☐ NK	 Exp. Date: / /	☐ Pre-Randomization ☐ Randomized → <u>Last Unit Given?</u> ☐ Yes ☐ No ☐ Post-Randomization ☐ Not Noted/Unknown
		/ /	:	___ ___ ___ ___	☐ Units ☐ ml.	☐ DO ☐ MR	☐ Aphaeresis ☐ Leuko-reduced ☐ NA ☐ NK ☐ Pooled ☐ Random	☐ Yes ☐ No ☐ NA ☐ NK	☐ Yes ☐ No ☐ NA ☐ NK	 Exp. Date: / /	☐ Pre-Randomization ☐ Randomized → <u>Last Unit Given?</u> ☐ Yes ☐ No ☐ Post-Randomization ☐ Not Noted/Unknown
		/ /	:	___ ___ ___ ___	☐ Units ☐ ml.	☐ DO ☐ MR	☐ Aphaeresis ☐ Leuko-reduced ☐ NA ☐ NK ☐ Pooled ☐ Random	☐ Yes ☐ No ☐ NA ☐ NK	☐ Yes ☐ No ☐ NA ☐ NK	 Exp. Date: / /	☐ Pre-Randomization ☐ Randomized → <u>Last Unit Given?</u> ☐ Yes ☐ No ☐ Post-Randomization ☐ Not Noted/Unknown
		/ /	:	___ ___ ___ ___	☐ Units ☐ ml.	☐ DO ☐ MR	☐ Aphaeresis ☐ Leuko-reduced ☐ NA ☐ NK ☐ Pooled ☐ Random	☐ Yes ☐ No ☐ NA ☐ NK	☐ Yes ☐ No ☐ NA ☐ NK	 Exp. Date: / /	☐ Pre-Randomization ☐ Randomized → <u>Last Unit Given?</u> ☐ Yes ☐ No ☐ Post-Randomization ☐ Not Noted/Unknown
		/ /		___ ___ ___ ___	☐ Units ☐ ml.	☐ DO ☐ MR	☐ Aphaeresis ☐ Leuko-reduced ☐ NA ☐ NK ☐ Pooled ☐ Random	☐ Yes ☐ No ☐ NA ☐ NK	☐ Yes ☐ No ☐ NA ☐ NK	 Exp. Date: / /	☐ Pre-Randomization ☐ Randomized → <u>Last Unit Given?</u> ☐ Yes ☐ No ☐ Post-Randomization ☐ Not Noted/Unknown
		/ /	:	___ ___ ___ ___	☐ Units ☐ ml.	☐ DO ☐ MR	☐ Aphaeresis ☐ Leuko-reduced ☐ NA ☐ NK ☐ Pooled ☐ Random	☐ Yes ☐ No ☐ NA ☐ NK	☐ Yes ☐ No ☐ NA ☐ NK	 Exp. Date: / /	☐ Pre-Randomization ☐ Randomized → <u>Last Unit Given?</u> ☐ Yes ☐ No ☐ Post-Randomization ☐ Not Noted/Unknown

Section 7.4 Instructions for Completing CRF Form # 8: Life Saving Interventions

Complete for all randomized subjects. Use this form to record lifesaving interventions (if applicable), from ED arrival through day 30 of hospitalization.

Record each event using the location and lifesaving intervention codes provided. Record the date and time in dd/mmm/yy and hh:mm formats.

If “other” is selected, record the information on form # 22.

Use the following codes to record unknown/missing data values:
NR = Not Recorded/Not Done NA = Not Applicable NK = Unknown

Source Documents: Hospital Medical Record.

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Form 8: Lifesaving Interventions *(Print additional pages if needed.)*

Check here ☐ if no lifesaving interventions were performed.

Location Codes (LOCAT)	
1	Emergency Department
2	Operating Room
3	Interventional Radiology
4	ICU
5	Intermediate Level Care
6	Nursing Unit
7	Other: *(Specify)*

Life Saving Interventions Codes	
1	Cardioversion
2	CPR
3	Emergency Laparotomy
4	Emergency Intubation
5	Chest Tube Insertion
6	Trach/Cricothyrotomy
7	Emergency Thoracotomy
8	Pericardiocentesis
9	Other *(Specify)*

LOCAT Code	**Start Date** *(dd/mmm/yy)*	**Start Time** *(hh:mm)*	**Intervention Code**
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
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	/ /	:	

Section 7.5 Instructions for Completing CRF Form # 9: Procoagulant Medications

Complete for all randomized subjects. Use this form to record procoagulant medications given (if applicable), from ED arrival through day 30 of hospitalization.

Record individual doses using the location and procoagulant medication codes provided. Record the start date and time in dd/mmm/yy and hh:mm formats.

If “other” is selected, record the information on form # 22.

Use the following codes to record unknown/missing data values:
NR = Not Recorded/Not Done NA = Not Applicable NK = Unknown

Source Documents: Hospital Medical Record.

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Form 9: Procoagulant Medications *(Record individual doses, print additional pages if needed)*

Check here ☐ if no procoagulant medications were given.

LOCATION CODE (LOCAT)	
1	Emergency Department
2	Operating Room
3	Interventional Radiology
4	ICU
5	Intermediate Level Care
6	Nursing Unit
7	Other *(Specify)*

Document Administration of the Following Medications Using the Codes Below	
1	Aminocaproic Acid *(Amicar) (g/hr.)*
2	Tranexamic Acid *(Cyclokapron) (mg/kg/hr.)*
3	Fibrinogen Concentrate *(Riastap) (mg/kg/hr.)*
4	Octaplex / Ocplex *(in ml.s)*
5	Prothrombin Complex Concentrate *(PCC)*
6	Recombinant Factor VIIa *(rFVIIa) (mics/kg)*
7	Factor VIII
8	Vitamin K
9	OTHER Procoagulant *(Specify with unit of measure)*

LOCAT	Administration Start Date *(dd/mmm/yy)*	Administration Start Time *(24hr clock in hh:mm)*	Medication Code *(If other, Specify)*	Dose Given
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___
	/ /	:		___ ___ ___

Section 7.6 Instructions for Completing CRF Form # 10: Operating Room Visits

Complete this form for all randomized subjects. Use the form to record operating room visits (if applicable), from ED arrival through day 30 of hospitalization.

Record the OR visit date and arrival into OR time in dd/mmm/yy and hh:mm formats. Indicate if the OR visit was planned or unplanned. An "unplanned" OR visit is defined as an emergent/urgent surgical procedure, and should also be listed on the AE/SAE form # 18. An OR visit directly from the ED on the day of admission (obviously unplanned), does not require documentation on the AE/SAE form # 18.

Record the PRIMARY surgical procedure using the codes provided, and any additional surgical procedure codes, if applicable.

If "other" is selected, record the information on form # 22.

Use the following codes to record unknown/missing data values:
NR = Not Recorded/Not Done NA = Not Applicable NK = Unknown

Source Documents: Hospital Medical Record.

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Completed By: ___ ___ ___

(Bar Code)

Form 10: Operating Room (OR) Visits

Check here ☐ if there were no OR visits

(Document OR visits from admission through Day 30 by date using the codes below. For OR visits during the initial resuscitation, also complete form #15. Print additional pages as needed.)

Surgical Procedure Codes

Head		**Surgical &/or Endoscopic Procedures Involving:**		**Pelvic Procedures**		**Upper Extremity Procedures**		**Lower Extremity Procedures**	
1	Craniotomy								
2	Craniectomy								
3	Subdural/Epidural Hematoma								
Neck									
4	Exploration of Neck	**10**	Esophagus	**18**	Closed Reduction	**25**	Amputation through the Forearm	**32**	Below Knee Amputation
		11	Stomach						
Chest		**12**	Small Intestine	**19**	Open Reduction/Internal Fixation	**26**	Amputation through the Humerus	**33**	Above Knee Amputation
5	Thoracotomy	**13**	Large Intestine	**20**	External Fixation	**27**	External Fixation of the Humerus	**34**	Closed Reduction/Internal Fixation
Abdomen		**Solid Organ Procedures**		**Damage Control Procedures**		**28**	External Fixation of the Forearm	**35**	Open Reduction/Internal Fixation
6	Exploratory Laparotomy	**14**	Liver	**21**	Abdominal Packing	**29**	Open Reduction/Internal Fixation	**36**	External Fixation of Tibia
Major Vascular Procedures		**15**	Kidney	**22**	Thoracic Packing	**30**	Closed Reduction/Internal Fixation	**37**	External Fixation of Femur
7	Artery/Vein Repair	**16**	Spleen	**23**	Vascular Shunt	**31**	Fasciotomy for Compartment Syndrome	**38**	Fasciotomy for Compartment Syndrome
Other Surgical Procedures		**17**	Pancreas	**24**	Temporary Abdominal Closure	**OR**	**Interventional Radiology Procedures →**	**39**	All IR Procedures Performed in the OR
8	Irrigation/Debridement								
9	Other *(Specify of form #22)*:								

"Unplanned" OR visits are defined as emergent/urgent surgical procedures. An OR visit on the day of admission from the ED does not need to be recorded on the AE/SAE Form #18. All other unplanned OR visits should be recorded on Form #18.

Record date in dd/mmm/yy format, and time using 24 hr. clock in hh:mm

OR Visit	Date of OR Visit	OR Arrival Time	Type of Visit?	**Primary** Surgical Procedure Code	Additional Surgical Procedure Code	Additional Surgical Procedure Code	Additional Surgical Procedure Code	Additional Surgical Procedure Code	Additional Surgical Procedure Code	Additional Surgical Procedure Code
1	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __	__ __

Section 7.7 Instructions for Completing CRF Form # 11: Interventional Radiology Visits

Complete this form for all randomized subjects. Record Interventional Radiology visits (if applicable), from ED arrival through day 30 of hospitalization.

Record the IR visit date and arrival into IR time in dd/mmm/yy and hh:mm formats. Indicate if the IR visit was planned or unplanned. An "unplanned" IR visit is defined as an emergent/urgent interventional radiology procedure, and should also be listed on the AE/SAE form # 18. An IR visit directly from the ED on the day of admission (obviously unplanned), does not require documentation on the AE/SAE form # 18.

Select the IR procedure performed from the list provided. Check all that apply.

If "other" is selected, record the information on form # 22.

Use the following codes to record unknown/missing data values:
NR = Not Recorded/Not Done NA = Not Applicable NK = Unknown

Source Documents: Hospital Medical Record.

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(Bar Code)

Form 11: Interventional Radiology (IR) Visit

Check here ☐ if there were no IR visits

(Document IR visits from admission through Day 30 by date using the codes below. For IR visits during the initial resuscitation, also complete form #15. Print additional pages as needed.)

Interventional Radiology Codes					
1	Craniocervical, Diagnostic	**6**	Hepatic, Therapeutic	**11**	Splenic, Diagnostic
2	Craniocervical, Therapeutic	**7**	Pelvic, Diagnostic	**12**	Splenic, Therapeutic
3	Extremity, Diagnostic	**8**	Pelvic, Therapeutic	**13**	Thoracoabdominal, Diagnostic
4	Extremity, Therapeutic	**9**	Renal, Diagnostic	**14**	Thoracoabdominal, Therapeutic
5	Hepatic, Diagnostic	**10**	Renal, Therapeutic	**15**	Other Angio Procedure: *(Describe on form # 22)*

IR Visit	Date of IR Visit *(dd/mmm/yy)*	IR Arrival Time *(24hr Clock in hh:mm)*	Type of Visit?	**Primary** IR Procedure Code	Additional IR Procedure Code	Additional IR Procedure Code	Additional IR Procedure Code	Additional IR Procedure Code	Additional IR Procedure Code
1	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __
	/ /	:	☐ Planned ☐ Unplanned	__ __	__ __	__ __	__ __	__ __	__ __

Section 7.8 Instructions for Completing CRF Form # 12: Clinical Lab Results

Complete this form for all randomized subjects and screening failures that have a research blood sample drawn. For randomized subjects, record clinical lab results from ED arrival through the initial 24 hours of hospitalization. For screening failures, record the results of any clinical labs collected at the same time as the research blood sample. Data collection is based on the subject's location during the 1st 24 hours. Record the 1st available lab results at each location, using the location codes provided.

It's unlikely that clinical test results collected at one time point will all be reported at the same time point. It isn't necessary to create new rows of data based on when the lab results were posted. Clinical lab results can be recorded on the same row based on the collection time of the sample.

Note: There are no protocol requirements for the clinical labs listed on form #12. We're capturing only standard of care lab data, if available.

Select the unit of measure for the lab tests indicated*. If "other" is selected, record the unit of measure in the space provided.
(mmol/L and mEq/L are equivalent)
(g/dL and gm/dL are equivalent)

Indicate if the sample was from an arterial or venous sample if applicable.

Indicate if the Base lab value is a deficit or excess.

FiO_2 Percentage can be estimated from the following oxygen delivery devices:

- Nasal cannula at 1L to 6L is 24% to 40%,
- Simple face mask with an oxygen flow rate of 5L to 15L is 28% to 50%,
- Non-rebreather mask with a minimum oxygen flow rate of 10L will deliver of 60% to 80%.

Source Documents: Hospital Medical Record.

The OpenClinica lab data fields will be limited to physiologically possible ranges, based on previous trauma study results.

Use the following codes to record unknown/missing data values:
NR = Not Recorded/Not Done NA = Not Applicable NK = Unknown

Print additional pages of the form as required.

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Study ID # ___ ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 12: Initial 24 hrs. Clinical Lab Results

(Record the first available lab results for the following tests at each location or location change for the 1st 24 hrs. following admission)

LOCATION CODE (LOCAT)			
1	Emergency Department	**5**	Intermediate Level Care
2	Operating Room	**6**	Nursing Unit
3	Interventional Radiology	**7**	Other *(Specify)*
4	ICU		

Section A: Pregnancy Test & Blood Type

LOCAT CODE	Date *(dd/mmm/yy)*	Time *(hh:mm)*	Lab Test		Results	Not Done
	/ /	:	Pregnancy Test	□ Blood □ Urine	□ Positive □ Negative □ Indeterminate	☐
	/ /	:	Blood Type	□ A Positive □ A Negative □ B Positive □ B Negative □ AB Positive □ AB Negative □ O Positive □ O Negative		☐

Section B: Blood Count & Coagulation Tests

***Indicate unit of measure, then enter value in the table below:**

Hgb? □ mmol/L □ g/dL □ g/L □ Other *(Specify)*:	**Fibrinogen?** □ mg/dL □ g/L □ Other *(Specify)*:	**Platelets?** □ x 10^3/µL □ x 10^9/L □ x 10^3/ ml^3 □ Other *(Specify)*:	**WBC?** □ x 10^3/µL □ x 10^9/L □ x 10^3/ mm^3 □ Other *(Specify)*:

LOCAT CODE	Date *(dd/mmm/yy)*	Time *(hh:mm)*	*Hgb	Hct %	*Platelets	*WBC	PT *(sec)*	PTT *(sec)*	INR	*Fibrinogen
	/ /	:	.	.	.	.	.	.	.	.
	/ /	:	.	.	.	.	.	.	.	.
	/ /	:	.	.	.	.	.	.	.	.
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	/ /	:	.	.	.	.	.	.	.	.
	/ /	:	.	.	.	.	.	.	.	.

(Print additional pages as needed.)

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Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 12: Initial 24hrs. Clinical Lab Results *(cont.)*

(Record the first available lab results for the following tests at each location or location change for the 1st 24 hrs. following admission)

LOCATION CODE (LOCAT)			
1	Emergency Department	**5**	Intermediate Level Care
2	Operating Room	**6**	Nursing Unit
3	Interventional Radiology	**7**	Other *(Specify)*
4	ICU		

Section C: Blood Gases

***Indicate unit of measure, then enter value in the table below:**

CO_2? □ mmol/L □ mg/L □ mEq/L □ Other *(Specify):*

HCO_3? □ mmol/L □ mg/L □ Other *(Specify):*

LOCAT CODE	Date *(dd/mmm/yy)*	Time *(hh:mm)*	Type of Blood Sample	FiO_2 %	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	*CO_2	*HCO_3	SaO_2 %	Base (mmol/L)	
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess
	/ /	:	□ Arterial □ Venous									□ Deficit □ Excess

(Print additional pages as needed.)

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CRF Version Date: 2012SEP05

Study ID # ___ ___ ___ ___ ___ ___ ___

Completed By: ___ ___ ___

(Bar Code)

Form 12: Initial 24hrs. Clinical Lab Results *(cont.)*

(Record the first available lab results for the following tests at each location or location change for the 1st 24 hrs. following admission)

LOCATION CODE (LOCAT)			
1	Emergency Department	5	Intermediate Level Care
2	Operating Room	6	Nursing Unit
3	Interventional Radiology	7	Other *(Specify)*
4	ICU		

Section D: Chemistry & Metabolic Panels

*** Indicate unit of measure, then enter value in the table below:**

Lactate? □ mg/dL □ mEq/L □ mmol/L □ Other *(Specify)*:
Creatinine? □ mg/dL □ µmol/L □ Other *(Specify)*:
Glucose? □ mg/dL □ mmol/L □ Other *(Specify)*:
Albumin? □ g/L □ U/L □ µmol/L □ g/dL □ Other *(Specify)*:
Total Bilirubin? □ mg/dL □ µmol/L □ Other *(Specify)*:

LOCAT CODE	Date (dd/mmm/yy)	Time (hh:mm)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	*Lactate	BUN (mg/dL)	*Creatinine	*Glucose	*Albumin	*Total Bilirubin	Bilirubin Direct, (mg/dL)	Bilirubin Indirect (mg/dL)	Calcium (mg/dL)
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.
	/ /	:	.	.	.	____ □ Arterial □ Venous	.	.	.		.	.	.	.

(Print additional pages as needed.)

Chapter 8 – Anesthesia

Section 8.1 Overview

The anesthesia record should be completed for randomized subjects with OR/IR visits during the first 24 hours of admission. Data collection is the responsibility of the anesthesia provider.

Section 8.2 Instructions for Completing CRF Form #15: Anesthesia Record

Question #1: Record the arrival date in dd/mmm/yy format.

Question #2: Record the arrival time in 24 hour clock hh:mm format.

Question #3: Select the location of the visit.

Question #4: Indicate if the subject was intubated before arrival to the OR/IR.

Question #5: Record the total dose for the pre-operative medications listed, or select none given or unknown.

Question #6: Record the total dose of medications for induction/intubation from the list provided, or select unknown.

Question #7: Record the total dose of IV medications given from the list provided during the OR/IR procedure.

Question #8: Record the maximum dose in percent for inhalation anesthetics listed during the OR/IR procedure.

Question #9: Record the blood pressure, pulse, SaO2 and ET CO2 at incision.

Question #10: Record the total dose of the medications listed during the OR/IR procedure.

Question #11: Indicate if the subject was mechanically ventilated. If "no" is selected, skip question # 9 and proceed to question # 13.

Question #12: Record the mechanical ventilation mode and initial settings.

Question #13: Indicate if ABG samples were sent during the OR/IR procedure. If "no" is selected, stop here.

Question #14: Record the last ABG results obtained during the OR/IR procedure. Indicate the lab unit of measure if indicated. If 'other' is selected, record the unit of measure in the space provided.
Note: Study Coordinators will be recording the 1st available ABG results obtained on arrival to OR/IR on form #12.

Use the following code for unknown data values:
NK= Unknown NR= Not Recorded/Not Done NA=Not Applicable

Form 15: Anesthesia Data Sheet

Check here ☐ if there were no OR/IR visits during the initial resuscitation.

*(Complete this form only for the **initial OR/IR visit** during the resuscitation period. This form should be completed by the Anesthesiologist.)*

1. Date of Visit: __ __ / __ __ __ / __ __
   (dd/mmm/yy format)

2. Arrival Time: ___ : ___
   (24hr Clock in hh:mm)

3. Subject Location: ☐ OR ☐ IR

4. Was the subject intubated before arrival in OR/IR? ☐ Yes ☐ No

5. Record the total dose of pre-operative medications administered before arrival in OR/IR.

   Check here ☐if no pre-operative medications were administered. **Check here** ☐if pre-operative medications are unknown.

Hypnotics	Total Dose	Analgesics	Total Dose	Benzodiazepines	Total Dose	NMB Agents	Total Dose
Etomidate	mg	Morphine	mg	Midazolam	mg	Succinylcholine	mg
Propofol	mg	Hydromorphone	mg	Lorazepam	mg	Vecuronium	mg
Ketamine	mg	Fentanyl	mcg			Rocuronium	mg

6. Record the total dose of medications administered for induction & intubation in the OR/IR.

   Check here ☐if medications are unknown.

Hypnotics	Total Dose	Analgesics	Total Dose	Benzodiazepines	Total Dose	NMB Agents	Total Dose
Etomidate	mg	Morphine	mg	Midazolam	mg	Succinylcholine	mg
Propofol	mg	Hydromorphone	mg	Lorazepam	mg	Vecuronium	mg
Ketamine	mg	Fentanyl	mcg			Rocuronium	mg

7. Record the total dose of I.V. medications administered during the OR/IR procedure.

Hypnotics	Total Dose	Analgesics	Total Dose	Amnestics	Total Dose	NMB Agents	Total Dose
Etomidate	mg	Morphine	mg	Midazolam	mg	Succinylcholine	mg
Propofol	mg	Hydromorphone	mg	Lorazepam	mg	Vecuronium	mg
Ketamine	mg	Fentanyl	mcg	Scopolamine	mg	Rocuronium	mg

Form 15: Anesthesia Data Sheet *(cont.)*

8. Record the maximum dose in % for the following inhalation anesthetics administered during the OR/IR procedure.

Sevoflurane	%	Desflurane	%	Isoflurane	%

9. Record the following data at incision.

Blood Pressure *(mmHg)*		Pulse *(beats/min)*	SaO_2 %	ET CO_2
Systolic	Diastolic			
___ ___ ___	___ ___ ___	___ ___ ___		

10. Record the total dose of vasopressors, inotropes, and chronotropes administered during the procedure.

Ephedrine	mg	Phenylephrine	mcg	Epinephrine	mg	Norepinephrine	mg	Atropine	mg

11. Was mechanical ventilation used? ☐ Yes *(proceed to next question)* ☐ No *(skip to question #13)*

12. Record the mechanical ventilation mode and initial settings.

Mode: ☐Volume Limited ☐Pressure Limited

Initial Settings: Tidal Volume _____ ml, Rate _____, FiO_2 _____, PEEP_____

13. Were ABG samples sent for analysis during the OR/IR visit?
☐ Yes *(proceed to next question)* ☐ No *(stop here)*

14. Record the LAST arterial blood gas results obtained during the procedure below.

***Indicate unit of measure, then enter value in the table below:**	
CO_2? ☐ mmol/L ☐ mg/L ☐ mEq/L ☐ Other *(Specify):*	**HCO_3?** ☐ mmol/L ☐ mg/L ☐ Other *(Specify):*

	Time *(hh:mm)*	FiO_2 %	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	*CO_2	*HCO_3	SaO_2 %	Base (mmol/L)	
LAST ABG	__ __ : __ __	_____	_____	_____	_____	_____	_____	_____	_____	☐ Deficit ☐ Excess

Chapter 9 - 24 hour to 30 day Follow-up Assessments

Section 9.1 Overview

Subject monitoring and data collection will continue until 1) it has been determined that the subject is not eligible for this trial, 2) the subject or LAR refuses continuation in the trial, 3) the subject has achieved hemostasis, 4) the subject has expired or 5) 24 hours have elapsed, whichever comes first. Until deemed ineligible, data from subjects will be collected and reviewed for screening purposes. Data on eligibility will be submitted to the HDCC to allow a description of screened versus enrolled subjects. For randomized subjects, data will be collected from a review of the medical records and results of diagnostic studies from admission until discharge or day 30 of the initial hospitalization.

For the subjects who are in the ICU/IMU setting:
Collect information on a daily basis using CRF Form # 16.

For the subjects who are on the floor (non monitored) setting:
Collect information 2 times a week (recommend Tuesday and Friday)
The 24 time period is based on a calendar day (i.e. 0000 to 2359)

Section 9.2 Instructions for Completing CRF Form #16: 24 hour to 30 day follow-up assessments

Complete this form for all randomized subjects. Use form # 16 to record daily assessments on subjects after the 1st 24hrs through day 30 of hospitalization (if applicable). Collect the information daily for ICU/IMU subjects & twice weekly thereafter until discharge or end of the study at day 30 of hospitalization. Collect all data elements from the previous 24 hours. If "highest" and "lowest" values are needed and only one value is available, enter the value in both data fields. Print a new form for each assessment.

The PROPPR protocol does not require any clinical labs to be ordered. Record lab results for the tests listed, if available. Site with subjects who have received hypertonic solutions during resuscitation may be prompted for additional sodium values, if available.

If the subject is intubated and has evidence of mild or moderate hypoxia, the site PI will review CXT/CT report or film to determine if bilateral infiltrates are present. Mild hypoxia is defined as a PaO2/FiO2 ratio <300 but ≥ 200 mmHg. Moderate hypoxia is defined as PaO2/FiO2 ratio < 200 mmHg.

The site PI's interpretation of CXR/CT information for

Question #1: Record the date the data values were obtained using dd/mmm/yy format. (The date should always be yesterday's date.)

Question #2: Indicate the subject's location.

Question #3: Record the highest and lowest values for vital signs and CVP/MAP readings during the previous 24 hrs. Indicate the unit of measure for temperature.

In the absence of an arterial line, MAP can be calculated according to this formula: MAP = [(2 x diastolic) +systolic] / 3

Question #4: Use the following key for GCS scoring. Record the total GCS if component scores are unavailable. For the purpose of GCS, the verbal score should

be "1" in the presence of an advanced airway.

GCS Scoring Key								
Eye Movement (E)	1	No Response	Verbal (V)	1	No Response / Intubated	Motor (M)	1	No Response
	2	To Pain		2	Incomprehensible Sounds		2	Extension *(Decerebrate)*
	3	To Verbal Command		3	Inappropriate Words		3	Flexion – *(Decorticate)*
	4	Spontaneous		4	Disoriented, Converses		4	Flexion – Withdrawals From Pain
				5	Oriented, Converses		5	Localizes Pain
							6	Obeys Commands Appropriately

Record the highest and lowest Apache score, if available. Indicate the Apache scoring system used.

Question #5: Record lab results for the tests listed if available. Record the highest and lowest values if available, or enter the same number for both values if only one test result is available. Select the unit of measure for the lab tests indicated*. If "Other" is selected, record the unit of measure in the space provided. Indicate if the Base lab value is a deficit or excess.

FiO_2 Percentage can be estimated from the following oxygen delivery devices:

- Nasal cannula at 1L to 6L is 24% to 40%,
- Simple face mask with an oxygen flow rate of 5L to 15L is 28% to 50%,
- Non-rebreather mask with a minimum oxygen flow rate of 10L will deliver of 60% to 80%.

Question #6: Indicate if ALI, ARDS, or pulmonary edema or contusions were suspected during the previous 24 hr. period. Record the site PI's assessment of CXR/CT information for the presence of bilateral infiltrates on intubated subjects displaying signs of mild or moderate hypoxia. Refer to the PROPPR Complications document for specific criteria, Section 12.3 of the PROPPR Manual of Operations. (Glue Grant & CDC complications definitions were used unless otherwise referenced).

Question #7: Indicate if the subject was mechanically ventilated during the preceding 24 hrs. Indicate if the subject was chemically paralyzed or received vasopressors. Paralytic drugs include Pancuronium Bromide, Rocuronium, Succinylcholine, or Vercuronium. Vasopressors include dobutamine, norepinephrine, ephedrine and Isoprel.

Question #8 : Record the total urine output for the previous 24 hrs.

Source Documents: Hospital Medical Record.

The OpenClinica lab data fields will be limited to physiologically possible ranges, based on previous trauma study results.

Use the following codes to record unknown/missing data values:
NA = Not Applicable (e-CRF code -995) ND = Not Detectable (e-CRF code -996)
NK = Unknown (e-CRF code -997) NP = Not Palpable (e-CRF code -998)
NR = Not Recorded/Not Done (e-CRF code -999)

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Form 16: 24 Hour to 30 Day Follow-Up Assessments

(*Complete daily while subject remains in the ICU/IMU & twice weekly thereafter until discharge or at Day 30 of hospitalization. Collect all data elements from the previous 24 hours. If a" highest" and "lowest" value is needed and only one value is available, enter the value in* ***both*** *data fields. Print a new form for each assessment.)*

Check here ☐ if the subject died within the 1st 24hr's and/or before reaching the ICU/IMU/Nursing unit and proceed to the next form.

1. Assessment Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Subject Location: ☐ ICU ☐ IMU *(Monitored Unit)* ☐ Nursing Unit

3. Vital Signs:

Systolic Blood Pressure *(mmHg)*	Highest Reading:	Lowest Reading:
Diastolic Blood Pressure *(mmHg)*	Highest Reading:	Lowest Reading:
Heart Rate *(bpm)*	Highest Reading:	Lowest Reading:
Respiratory Rate	Highest Reading:	Lowest Reading:
Temperature ☐ F. ☐ C.	Highest Reading:	Lowest Reading:
CVP *(mmHg)*	Highest Reading:	Lowest Reading:
Mean Arterial Pressure *(MAP) (mmHg)*	Highest Reading:	Lowest Reading:

4. GCS and APACHE Scores:

(Record APACHE score if available)

Glasgow Coma Scale *(Record individual assessment scores or the GCS total)*		*Highest Score*	*Lowest Score*
	Eye Movement:		
	Verbal:		
	Motor:		
	GCS Total:		

APACHE *(select Scoring System)*	*Highest Score*	*Lowest Score*
☐ APACHE II		
☐ APACHE III		
☐ APACHE IV		

5. Lab Assessments:

Arterial Blood Gases	pH	Highest Reading:	Lowest Reading:
	FiO_2 *(for intubated patients)*	Highest Reading:	Lowest Reading:
	PaO_2	Highest Reading:	Lowest Reading:
	PaO_2 / FiO_2 Ratio *Corresponding values from the same time point.* ****Mild hypoxia*** *is defined as a PaO_2 / FiO_2 ratio <300 but ≥200,* ****Moderate hypoxia*** *is defined as a PaO_2 / FiO2 ratio < 200 mmHg*	Highest Reading:	Lowest Reading:
	$PaCO_2$	Highest Reading:	Lowest Reading:
	CO_2 ☐ mmol/L ☐ mg/L ☐ mEq/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	SaO_2 %	Highest Reading:	Lowest Reading:
	HCO_3 ☐ mmol/L ☐ mg/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Base *(mmol/L)* ☐ Deficit ☐ Excess	Highest Reading:	
	Base *(mmol/L)* ☐ Deficit ☐ Excess	Lowest Reading:	

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Form 16: 24 Hour to 30 Day Follow-Up Assessments *(cont.)*

5. Lab Assessments: *(cont.)*

Coagulation	PT *(seconds)*	Highest Reading:	Lowest Reading:
	PTT *(seconds)*	Highest Reading:	Lowest Reading:
	INR *(seconds)*	Highest Reading:	Lowest Reading:
	Fibrinogen ☐ mg/dL ☐ g/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:

Blood Count	Hgb *(Select measure)* ☐ mmol/L ☐ g/dL ☐ g/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Hematocrit *(Hct %)*	Highest Reading:	Lowest Reading:
	WBC Count *(Select measure)* ☐ x 10^3/µL ☐ x 10^9/L ☐ x 10^3/ mm^3 ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Platelets *(Select measure)* ☐ x 10^3/µL ☐ x 10^9/L ☐ x 10^3/ml^3 ☐ Other *(specify):*	Highest Reading:	Lowest Reading:

Chemistry & Metabolic Values	Sodium *(mEq/L)*	Highest Reading:	Lowest Reading:
	Potassium *(mEq/L)*	Highest Reading:	Lowest Reading:
	Chloride *(mEq/L)*	Highest Reading:	Lowest Reading:
	BUN *(mg/dL)*	Highest Reading:	Lowest Reading:
	Creatinine *(Select measure)* ☐ mg/dL ☐ µmol/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Albumin *(Select measure)* ☐ g/L ☐ g/dL ☐ U/L ☐ µmol/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Glucose *(Select measure)* ☐ mg/dL ☐ mmol/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Lactate *(Select measure)* ☐mg/dL ☐mEq/L ☐mmol/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Total Bilirubin *(Select measure)* ☐ mg/dL ☐ µmol/L ☐ Other *(specify):*	Highest Reading:	Lowest Reading:
	Calcium *(mg/dL)*	Highest Reading:	Lowest Reading:

6. Was the subject thought to have any of the following?

Acute Lung Injury *(ALI)*?	☐ Yes, *(Document on AE/SAE form 18)* ☐ No
Acute Respiratory Distress Syndrome *(ARDS)*?	☐ Yes, *(Document on AE/SAE form 18)* ☐ No
Pulmonary edema/respiratory failure from cardiac origin?	☐ Yes ☐ No
Pulmonary Contusions?	☐ Yes ☐ No
If intubated and displaying mild or moderate hypoxia *, does today's CXR/CT demonstrate bilateral infiltrates?	☐ Yes ☐ No ☐ NA

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7. Did the subject require any of the following?

Mechanically Ventilated?	☐ Yes ↓ ☐ No ***(Enter ventilator settings below associated with the LOW PaO_2 / FiO_2 Ratio recorded above)***
Mode: ☐ Volume Limited ☐ Pressure Limited Tidal Volume: ml Rate: FiO_2: PIP: PEEP:	
Chemical Paralysis?	☐ Yes ☐ No
Vasopressors?	☐ Yes ☐ No
Dialysis?	☐ Yes ☐ No

8. Urine Output for the last 24 hours: ___ ___ ___ ___ *(ml.s)*

Section 9.3 Follow-up Process after Hospital Discharge

Day Follow-Up
Data will be collected on a daily basis for 30 days of hospitalization or until discharge/death on all subjects who have consented to continue in the trial.

Attempts to Contact Subject and/or LAR
If discharge occurs before hospital day 30 and the subject is discharged to a hospice, nursing home or other healthcare provider, research staff will contact the facility to ascertain the subject's vital status. If the subject was discharged to his/her usual residence before day 30, the research staff will contact the subject or their family/legally authorized representative (LAR). For subjects discharged to another facility, the clinical research staff should complete an authorization form to release protected health information (PHI) and obtain signatures from the subject or LAR prior to discharge. A copy of the signed authorization form and study consent will be provided to the facility for release of PHI. Clinical sites will follow local and state HIPPA guidelines for release of PHI for research. A sample consent for release of PHI is included at the end of this chapter.

The State Death Index and other Sources of Vital Statistics
If vital status remains unknown the clinical site will request periodic searches for the subject's social security number in the Social Security Master Death Index, the respective State Health Department's vital statistics/mortality database, and the mortality databases of a credit reporting agency, e.g., Experian. For subjects not reported as deceased by these sources by day 30 following ED admission, batch searches of the mortality databases will continue every quarter until trial close-out. Date (and cause of death when available) for out-of-hospital deaths will be documented; however, underlying and contributing causes of death may not be available from these sources.

Section 9.3.1 Instructions for Completing CRF Form #17: Discharge/Death

Use form #17 to record discharge or death information on enrolled subjects. The source documents for this form include the hospital medical record, direct communication with the subject or LAR and documented in the clinical note or on CRF, forms # 19, 20 and 22, death registry and/or other public sources.

Question #1: Record the total cumulative number of ICU days. There are no qualifying ICU time limits for the stay to count as an ICU day. A subject admitted to the ICU at 23:55 will be credited with one ICU day for the 5 minutes they spent in the ICU.

Question #2: Record the total cumulative number of ventilator days using the same formula as above.

Question #3: Record the subject's insurance status on admission.

Question #4: Record the subject's insurance status at discharge, death, or Day 30 of the protocol if still hospitalized.

Question #5: Indicate if the subject was on anti-coagulants prior to the injury. If "yes" is selected, indicate the anti-coagulant drug from the list provided.

Question #6: Indicate if the subject had a past medical history of any of the listed conditions/diseases. Select all that apply.

Question #7: Indicate if DNR was ordered at any point during the hospitalization. If "yes" is selected, record the date and time in dd/mmm/yy and mm:hh formats.

Question #8: Indicate if care was withdrawn at any point during the hospitalization. If "yes" is selected, record the date and time in dd/mmm/yy and mm:hh formats.

Question #9: Indicate if the subject **died before** Day 30 of the protocol. If "yes" is selected, skip questions 10 through 14 and proceed to question #15 on this form. If "no" is selected, proceed to the next question.

Question #10: Record the date of discharge in dd/mmm/yy format or select the "remains hospitalized option (if applicable). If "remains hospitalized" is selected, skip questions 11 through 14 and proceed to question # 15 on this form. If the subject was discharged, proceed to the next question.

Question #11: Record the first 15 discharge diagnostic and procedure codes in order as listed in the subjects medical record.

Question #12: Indicate if the subject left AMA.

Question #13: Choosing from the list provided, indicate where the subject went at discharge.

Question #14: Record a discharge GCS if available. Record the total GCS if component scores are unavailable.

Use the following key for GCS scoring.

GCS Scoring Key								
Eye Movement (E)	1	No Response	**Verbal (V)**	1	No Response / Intubated	**Motor (M)**	1	No Response
	2	To Pain		2	Incomprehensible Sounds		2	Extension *(Decerebrate)*
	3	To Verbal Command		3	Inappropriate Words		3	Flexion – *(Decorticate)*
	4	Spontaneous		4	Disoriented, Converses		4	Flexion – Withdrawals From Pain
				5	Oriented, Converses		5	Localizes Pain
							6	Obeys Commands Appropriately

Question #15: Record the extended Glasgow outcome scale (GOSE) if available.

Question #16: Enter the Abbreviated Injury Score (AIS) score if available. Use the scoring key provided to indicate the worst injury for each anatomical region listed. If no injuries were sustained in the anatomical region, enter zero.

AIS SCORE	
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Unsurvivable

ANATOMIC REGION	**INJURY# 1 Score**
Head	
Neck	
Face	
Chest	
Abdomen	
Extremity	
External	

Question #17: Record the Injury Severity Score (ISS), if available.

Question #18: Record the date the subjects' vital status (dead or alive) was confirmed using dd/mmm/yy format

Question #19: Choosing from the list provided, indicate the source of the vital status information.

Question #20: Record the subject's vital status on Day 30 following the initial hospitalization. If "deceased" is selected, proceed to the next question on this form. If "living" or "lost to follow-up" is selected, stop here and proceed to the next form.

Question #21: Choosing from the list provided, indicate the subject's location at the time of death. If "other" is selected, record the information on form # 22.

Question #22: Record the date of death using dd/mmm/yy format. The "unknown" option will only be available for subjects who die after discharge. Death adjudication packets should be submitted to the HDCC for in-hospital deaths. The adjudication packet is not required for deaths occurring after discharge. Refer to Section 12.7 for more information.

Question #23: Record the time of death using hh:mm format. The "unknown" option will only be available for subjects who die after discharge.

Question #24: Record the Principal Investigator's determination of cause of death from the list provided. Check all that apply. If "other" is selected, record the information on from # 22. See Section 12.6 for cause of death definitions.

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Form 17: Discharge/Death *(Initial Hospitalization through Day 30 of the PROPPR Protocol)*

1. Total (cumulative) number of ICU days: ___ ___

2. Total (cumulative) number of ventilator days: ___ ___

3. Insurance status on admission: *(Select one)*

□ Self Pay/None □ Private Insurance □ Medicare/Medicaid
□ Not Noted/Unknown □ Military Provider □ NA *(Canada Site Only)*

4. Insurance status at discharge, death, or Day 30 of protocol if still hospitalized: *(Select one)*

□ Self Pay/None □ Private Insurance □ Medicare/Medicaid
□ Not Noted/Unknown □ Military Provider □ NA *(Canada Site Only)*

5. Was there a reported history of anti-coagulant use prior to the injury?

□ Yes ↓ □ No □ Not Noted/Unknown

□ Warfarin □ Plavix □ Aspirin □ Thrombin Inhibitors □ Other, specify: _____

6. ***Prior to trauma***, was there a reported history of any of the following? *(Check all that apply)*

□ Alcohol Use
□ Acquired Immune Deficiency Syndrome *(AIDS)*
□ Cardiovascular Disease
□ Cirrhosis
□ COPD
□ Diabetes
□ Hepatic Failure
□ Hypertension
□ Immunosuppression
□ Leukemia/Multiple Myeloma
□ Lymphoma
□ Metastatic Cancer
□ Renal Disease
□ Tobacco Use *(smoking)*

7. Was a DNR ordered at any point during the hospitalization? □ Yes ↓ □ No
Time: ___:___ □ Unknown
(24hr Clock in hh:mm)
Dated: ___ / _____ / ___
(dd/mmm/yy)

8. Was care withdrawn at any point during the hospitalization? □ Yes ↓ □ No
Time: ___:___ □ Unknown
(24hr Clock in hh:mm)
Dated: ___ / _____ / ___
(dd/mmm/yy)

9. Did the subject die before day 30 of the initial hospitalization? □ Yes *(Go to question # 15)*
□ No *(Go to next question)*

10. Date of hospital discharge: ___ / _____ / ___ □ Remains Hospitalized on Day 30.
(dd/mmm/yy) *(Go to question #16)*

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CRF Version Date: 2013 MAR 01 Completed By: ___ ___ ___

Form 17: Discharge/Death *(Initial Hospitalization through Day 30 of the PROPPR Protocol, cont.)*

11. Record the ***first*** 15 discharge diagnostic and procedure codes below.

Discharge Diagnostic Codes *(xxx.xx format)*		Procedure Codes *(xx.xx format)*	
(1) __ __ __ . __ __	(8) __ __ __ . __ __	(1) __ __ . __ __	(9) __ __ . __ __
(2) __ __ __ . __ __	(10) __ __ __ . __ __	(2) __ __ . __ __	(10) __ __ . __ __
(3) __ __ __ . __ __	(11) __ __ __ . __ __	(3) __ __ . __ __	(11) __ __ . __ __
(4) __ __ __ . __ __	(12) __ __ __ . __ __	(4) __ __ . __ __	(12) __ __ . __ __
(5) __ __ __ . __ __	(13) __ __ __ . __ __	(5) __ __ . __ __	(13) __ __ . __ __
(6) __ __ __ . __ __	(14) __ __ __ . __ __	(6) __ __ . __ __	(14) __ __ . __ __
(7) __ __ __ . __ __	(15) __ __ __ . __ __	(7) __ __ . __ __	(15) __ __ . __ __
(8) __ __ __ . __ __		(8) __ __ . __ __	

12. Did the subject leave AMA? □ Yes □ No

13. Subject discharged to?: *(Select one)*

□ Home □ Long Term Care Facility □ Skilled Nursing Facility
□ Rehabilitation Facility □ Hospice □ Acute Care Hospital
□ Other, specify: _____

14. Was a Discharge Glasgow Coma Score (GCS) obtained?

□Yes ↓ □ No

GCS Score E: ___, V: ___, M: ___ or GCS Total Score if Component Scores Unknown: ___

GCS Scoring Key								
Eye Movement	1	No Response	Verbal	1	No Response / Intubated	Motor	1	No Response
	2	To Pain		2	Incomprehensible Sounds		2	Extension (Decerebrate)
	3	To Verbal Command		3	Inappropriate Words		3	Flexion – (Decorticate)
	4	Spontaneous		4	Disoriented, Converses		4	Flexion – Withdrawals From Pain
				5	Oriented, Converses		5	Localizes Pain
							6	Obeys Commands Appropriately

15. Was an extended Glasgow outcome scale (GOSE) obtained?

□ Yes, GOSE Score: _____ □ No

The Extended Glasgow Outcome Scale (GOSE) Scoring Key	
SCORE	Performance Level
1	Dead
2	Vegetative State
3	Lower severe disability; completely dependent on others
4	Upper severe disability; dependent on others for some activities
5	Lower moderate disability; unable to return to work or participate in social activities
6	Upper moderate disability; return to work at reduced capacity, reduced participation in social activity
7	Lower good recovery; good recovery with minor social or mental deficits
8	Upper good recovery

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2013 MAR 01 Completed By: ___ ___ ___

Form 17: Discharge/Death *(Initial Hospitalization through Day 30 of the PROPPR Protocol, cont.)*

16. Abbreviated Injury Scale (AIS) Score: **Check here** □ if the AIS Score was not noted/unknown.

ANATOMIC REGION	Head	Neck	Face	Chest	Abdomen	Extremity	External
INJURY# 1 Score							

17. Injury Severity Score (ISS): __ __ __ __ **Check here** □ if the ISS Score was not noted/unknown.

18. Date the 30 Day status information was confirmed *(Subject living or deceased)*: ____ /_____ /____
(dd/mmm/yy)

19. Source of Information: *(Select one)*
□ Medical Record □ Subject (self-report) □ Family/LAR
□ Other Healthcare Facility □ Vital Statistics/Death Registry
□ Other *(Specify)*: _____ □ Direct Observation

20. Subject status (primary outcome measure) 30 days after the initial hospital admission:

□ Deceased *(Go to next question)*
□ Living *(Stop here, this form is complete)*
□ Unknown/Lost to Follow-Up *(Stop here, this form is complete)*

21. Subject Location at time of death:

□ Home/Other Healthcare Facility □ ED □ OR □ IR □ ICU
□ Intermediate Level Care □ Nursing Unit □ Other *(Specify):* _____
□ Location Unknown/Information from Registry Database

22. Date of Death: ____/_____/____ □ Unknown *(Option available **only** for subjects who die **after** discharge)*
(dd/mmm/yy)

23. Time of Death: ___:___ □ Unknown *(Option available **only** for subjects who die **after** discharge)*
(24hr Clock in hh:mm)

24. Cause of Death: *(Check ALL that apply)*

□ Exsanguination / Hemorrhagic Shock
□ Traumatic Brain Injury (TBI)
□ Respiratory/Pulmonary Contusion/Tension Pneumothorax
□ Sepsis
□ Multiple Organ Failure (MOF)
□ Cardiovascular Event *(Select event(s) from below)*
○ Stroke ○ MI ○ Both Stroke & MI
□ Pulmonary Embolism
□ Transfusion Related Fatality
□ Other, *(Specify)*: _____
□ Unknown

Section 9.3.2 Sample Consent for Release of PHI

Permission to Disclose and use Personal Health Information for Research

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

Please Note: Any time the words "you" or "your" appear in this document, it could apply to you if you are the research study participant OR to your legally authorized representative.

A. What is the purpose of this form?

You previously consented to participate in the PROPPR research study following a traumatic injury that required hospitalization, and you have been discharged to another healthcare facility within 30 days of the initial trauma injury. The purpose of this form is to obtain your permission for the PROPPR research team to continue collecting information on your health status and the medical care you have received up to day 30 following the trauma injury. State and federal privacy laws protect the use and release of your health information. Under these laws, your health care provider cannot release your health information to the research team unless you give your permission. The research team includes the researchers and people hired by the University or the sponsor to do the research. This form describes the different ways that the researcher, research team and research sponsor may use your health information for the research study. *The research team will use and continue to protect your information as described in the* attached study consent form you previously signed. *If you have questions, please ask a member of the research team at [insert local contact telephone number].*

B. What Personal Health Information will be released?

If you give your permission and sign this form, you are allowing *[insert name of healthcare provider(s)/facility releasing medical records]* to release the following medical records containing your Personal Health Information. Your Personal Health Information includes health information in your medical records and information that can identify you. For example, Personal Health Information may include your name, address, phone number or social security number.

☐ Entire Medical Record	☐ Radiology Reports	☐ Laboratory Reports
☐ Outpatient Clinic Records	☐ Progress Notes	☐ History & Physical Exams
☐ Consultations	☐ Diagnostic Imaging Reports	☐ Pathology Reports
☐ Discharge Summaries	☐ Other: _____	

C. Who will view my Personal Health Information?

Your Personal Health Information may be released to the following individuals associated with the research study:

1. To the research team for the research described in the attached study consent form;
2. To others who are required by law to review the quality and safety of the research, including: U.S. government agencies, such as the Food and Drug Administration, the research sponsor or the sponsor's representatives. These organizations and their representatives may see your Personal Health Information. They may not copy or take it from your medical records unless permitted or required by law.

D. How will my Personal Health Information be used in research reports?

Research report will ***not*** include your name, address, or telephone or social security number. The research report may include your date of birth, and dates you received medical care. The research report will

also include information the research team collects in the study. The research team and the research sponsor may use the research report and share it with others in the following ways:

1. To perform more research;
2. Share it with researchers in the U.S. or other countries;
3. Place it into research databases;
4. Use it to improve the design of future studies;
5. Use it to publish articles or for presentations to other researchers;
6. File applications with U.S. government agencies for approval of new treatment methods.

E. Does my permission expire?

This permission to release your Personal Health Information expires when the research ends and all required study monitoring is over. Research reports can be used forever.

F. Can I cancel my permission to release Personal Health Information?

You can cancel your permission at any time. You can do this in two ways. You can write to the researcher or you can ask someone on the research team to give you a form to fill out to cancel your permission. If you cancel, information that was already collected and disclosed about you may continue to be used. Also, if the law requires it, the sponsor and government agencies may look at your medical records to review the quality or safety of the study.

G. Signature?

If you agree to the release and use of your Personal Health Information, please sign below. You will be given a signed copy of this form.

_____

Name of Subject (print)

_____ _____

Signature of Subject Date

_____ _____

Name of Legally Authorized Representative (print) Relationship to Subject

_____ _____

Signature of Legally Authorized Representative Date

Chapter 10 - CRF Form # 22: Additional Information

Section 10.1 Overview

This form is optional. Record additional information or select the box at the top of the form if there are no additional comments. Reference the information to a specific CRF form number and question if applicable. Print additional pages if needed.

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012JUL25 Completed By: ___ ___ ___

Form 22: Additional Information **Check here** ☐ if there are no additional comments.

Form #	Question #	Comments

(Print additional pages if needed)

Chapter 11 – Trauma Registry Data

Section 11.1 Overview

Complete this form for all screening failures. Indicate if trauma registry data will be available.

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2013 MAR 01 Completed By: ___ ___ ___

Form 23: Trauma Registry Data Form *(Complete this form for all screening failures.)*

1. Was subject data entered into the trauma registry? ☐ Yes ☐ No

Chapter 12 Safety Monitoring

Section 12.1 Serious Adverse Events Monitoring

Objectives
To describe the procedures by which Serious Adverse Event (SAE) notifications are received from PROPPR clinical centers, processed by the HDCC, and reported to the NHLBI and the DSMB.

Scope
This SOP applies to all HCCC/HDCC personnel monitoring receipt of SAE Reports.

References
CFR 312.32 – IND Safety Reports
CFR 312.44 – Termination
CFR 312.50 – General Responsibilities of Sponsors
CFR 312.56 – Review of Ongoing Investigations
CFR 312.64 – Investigator Reports
Guideline for Good Clinical Practice [ICH E6(R1)], Section 4.4 – Communication with IRB/IEC
Guideline for Good Clinical Practice [ICH E6(R1)], Section 4.11 – Safety Reporting
Guideline for Good Clinical Practice [ICH E6(R1)], Section 5.16 – Safety Information
Guideline for Good Clinical Practice [ICH E6(R1)], Section 5.17 – Adverse Drug Reaction Reporting
FDA Guidance: MedWatch Form 3500A, November 2005
FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs- Improving Human Subjects Protection, January 2009
FDA Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, September 2010

Definitions
AE—Adverse Event
HDCC—Houston Data Coordinating Center
HDCC PI—Data Coordinating Center Principal Investigator
DSMB—Data Safety Monitoring Board
FDA—Food and Drug Administration
IRB – Institutional Review Board
NHLBI--- National Heart, Lung, and Blood Institute
SAE—Serious Adverse Event

Responsibilities
The HDCC PI, Independent Medical Monitor, Study Monitors, and HDCC Program Manager review incoming SAE reports for content and appropriateness.

The HDCC program manager triages the incoming reports and if necessary contacts the site coordinator for additional information. Based on new information, the independent medical monitor has the authority to upgrade or downgrade the severity of the event and make independent assessments regarding the possible relatedness to the intervention based on information available in the Investigators Brochure, the study protocol, and the informed consent.

The HDCC program manager is responsible for submitting SAE reports to the NHLBI/DSMB within required timelines.

The Study Monitors confirm source with eCRF submissions for events previously reported. Should new events be identified during a study monitoring visit, submissions will be requested by the Study Monitor and additional documentation collected.

The independent medical monitor will review all unexpected and possibly related SAEs and provide an unbiased written assessment of the event. At a minimum, the medical monitor will comment on the relationship of the SAE to participation in the trial. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the site PI.

The HDCC Program Manager is responsible for assembling cumulative reports of all SAEs to meet requirements as mandated by the FDA, Health Canada, DSMB, and IRBs of the DCC and clinical centers. Events that meet the FDA reporting guidelines are submitted as IND Safety Reports using the MedWatch form.

Procedures
Refer to the PROPPR Safety Monitoring Plan in the following section.

Section 12.2 Safety Monitoring Plan

SAFETY MONITORING PLAN

Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)

Data Coordinating Center
PI: and Director: Barbara C. Tilley, Ph.D.
Co-Director and Biostatistician: Sarah Baraniuk, Ph.D.
Programmer Analyst: Xuemei Xi, MS
Clinical Trial Program Manager: Steven Kosmach, MSN, RN, CCRC
Regulatory Coordinator: Maryann Murray, BS, CCRC
UTHealth, School of Public Health
Houston, TX 77030

Clinical Coordinating Center
PI and Lead Investigator: John Holcomb, MD
Co-Investigator: Charles Wade, Ph.D.
Co-Investigator: Deborah del Junco, Ph.D.
Clinical Trial Program Manager: Jeanette Podbielski, BSN, RN
UTHealth, Medical School
Houston, TX 77030

ROC Data Coordinating Center
PI: Gerald van Belle, PhD.
Co-Investigator: Brian Leroux, PhD.
Trauma Project Manager: Kellie Sheehan, BSN, RN
University of Washington
Seattle, WA 98195

August 29th, 2012

Table of Contents

1 List of Abbreviations

AE	Adverse Event
AKI	Acute Kidney Injury
ALI	Acute Lung Injury
ADRs	Adverse Drug Reactions Form *(Health Canada)*
ARDS	Acute Respiratory Distress Syndrome
CRF	Case Report Form
DVT	Deep Vein Thrombosis
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	US Food and Drug Administration
HCCC	Houston Clinical Coordinating Center
HCCC PI	Houston Clinical Coordinating Center Principle Investigator
HDCC	Houston Data Coordinating Center
HDCC PI	Houston Data Coordinating Center Principle Investigator
IRB	Institutional Review Board
MI	Myocardial Infarction
MOF	Multi-Organ Failure
NHLBI	National Heart, Lung, and Blood Institute
PE	Pulmonary Embolus
PI	Principal Investigator
REB	Research Ethics Board
SAE	Serious Adverse Event
TRALI	Transfusion Related Acute Lung Injury
VAP	Ventilator Assisted Pneumonia

2 Responsibilities

Clinical Site PIs and study coordinators are responsible for reporting initial and follow-up SAE information in an accurate and timely manner, and reporting SAE's to the local IRB/REB within the time frame specified by local IRB/REB policy. SAE's will be documented in the subject's eCRF, and on a FDA MedWatch 3500 or Health Canada ADRs form, completed by the clinical site PI/Study Coordinator.

The HDCC will review all incoming reports for content and appropriateness on a daily basis, and if necessary contact the site coordinator for more information. AE/SAE events entered into OpenClinica will generate an automated e-mail notification to the HCCC & HDCC program managers, the HCCC PI (or designee), and the Independent Medical Monitor (see Appendix A). Events meeting FDA *(or Health Canada)* reporting guidelines will be submitted as an IND Safety Report using the MedWatch 3500 form or the Health Canada ADRs forms, (Appendix B & C). The HDCC will forward the SAE Report to the HCCC PI (or designee) and independent Medical Monitor for initial review.

The HCCC PI (or designee) will review all unexpected, related SAE individually and comment on the relationship of the SAE to participation in the trial. The HCCC PI will also indicate whether he concurs with the details of the report provided by the site PI. All other AE/SAE events will be reported in aggregate (blinded) for review by the HCCC PI on a monthly basis. The HCCC PI will also review aggregate (blinded) DSMB reports.

The independent medical monitor will review all unexpected and possibly related SAEs and provide an unbiased written assessment of the event. At a minimum, the medical monitor will comment on the relationship of the SAE to participation in the trial. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the site PI. The independent medical monitor will review aggregate (blinded) DSMB reports and the study records of any subject removed from the study due to safety concerns.

The HCCC will issue a report to the NHLBI/DSMB, FDA, Health Canada, and participating clinical site PIs, that will include a statement on the status of information known about the SAE event; preliminary report, follow-up report, or a final report (see sample cover letters, Appendix D and E).

The HCCC will issue follow-up reports to the NHLBI/DSMB, FDA, Health Canada, and participating clinical site PIs when relevant new information becomes available.

The HDCC Program Manager will be responsible for MedDRA coding of the MedWatch 3500 form *(or equivalent Health Canada form, if applicable),* and assembling cumulative reports of all SAEs to meet requirements as mandated by the FDA, Health Canada, the DSMB, and IRBs/REBs of the HDCC and clinical sites.

Study Monitors will confirm source documents with eCRF submissions for all SAEs previously submitted. The study monitor will request submission of any new events identified during a monitored visit. The study monitor will verify site IRB/REB submissions involving SAEs (per local IRB/REB reporting requirements) and DSMB reports.

3 Adverse Events

Expected Adverse Events
Common expected AEs/SAEs will include: trauma injury related infections, transfusion-related acute lung injury (TRALI), ventilator associated pneumonia (VAP), thrombotic complications (DVT, PE, MI, stoke), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), multiple organ failure (MOF) and intracranial operative interventions.

Adverse Events Reporting Procedure
All adverse events will be classified by: a) severity (AE, SAE); b) expected vs. unexpected; and c) related vs. unrelated. Unrelated, non-serious adverse events, either expected or unexpected (as determined by the site PI), will not be recorded on eCRF. Only study related adverse events or ancillary outcomes measures of interest (see section 6.2 of protocol) that occurred during the study period (after randomization until study conclusion) will be recorded.

4 Serious Adverse Events

Expected, Serious Adverse Events
The study population is expected to have a large number of unrelated, expected serious adverse events including death from trauma related injuries. The SAE will be recorded on the subject's eCRF and reported as per local IRB/REB requirements.

Unexpected, Serious Adverse Events:
Potential transfusion related serious adverse events will include transfusion-related death and/ or, re-hospitalizations, or other unexpected SAEs. The site PI will classify the relatedness of the SAE to the study intervention.

Serious Adverse Events Reporting Procedure

SAE reporting for the PROPPR study will follow the FDA guidance on safety reporting requirements for IND and BA/BE studies dated September, 2010. In addition to following local reporting procedures, clinical sites will notify the HCCC/HDCC of a possible transfusion-related death within three business days of discovery of the event and complete a MedWatch 3500 or Health Canada ADRs form. The HCCC/HDCC will report transfusion related deaths to the DSMB, FDA, Health Canada, NHLBI, and IRBs/REBs within seven calendar days of receiving the site report. All other unexpected and possibly related SAEs will be reported within 15 calendar days of receiving the site report.

Additional blood donor information will be collected for subjects who experience transfusion related acute lung injury (TRALI). The blood donor information will be collected from the site blood bank and will include gender and donor transfusion history.

Clinical Sites will provide sodium levels for subject's experiencing hypernatremia associated with use of hypertonic saline products.

5 Cause of Death Adjudication

All subject deaths will be assigned to one or more of the following groups: Exsanguination/Hemorrhagic Shock, Traumatic Brain Injury (TBI), Respiratory/Pulmonary Contusion/Tension Pneumothorax, Sepsis, Multi Organ Failure (MOF), Cardiovascular Event, Pulmonary Embolism, Transfusion Related Fatality, or other, unknown. In the event of a subject death, the local site PI will determine the cause of death using the categories mentioned above. The cause of death assessment will be forwarded to the HDCC for review. Timing of the withdrawal of care (if applicable); will be noted in the assessment.

The HCCC PI will review the cause of death assessment and all available de-identified clinical documents such as the initial H&P, operative notes, discharge summary, death note, etc. The HCCC PI will remain blinded to the PROPPR group assignment. The HCCC PI will determine the cause of death using the categories mentioned above and will forward the report to the HDCC.

The HDCC will compare the Site PI and HCCC PI cause of death assignments, and if in agreement, will be accepted as the cause of death for that individual subject. If there is disagreement for cause of death, the same redacted and de-identified information will be forwarded to the Medical Monitor for review. The Medical Monitor can discuss the case with either the Site or HCCC PI, but must remain blinded to the PROPPR treatment group assignment. The Medical Monitor's assessment will be considered the final cause of death for that individual subject.

The adjudication process described above will be used for all clinical sites with the exception of the Houston clinical site. The Medical Monitor will review the site PIs cause of death assignment. The Medical Monitors assessment will be considered final. The HCCC PI will not participate in death adjudication for Houston subjects.

Cause of deaths requiring adjudication from the Medical Monitor will be summarized and reported in aggregate to the DSMB.

6 DSMB Reports

Summary statistics of adverse events will be reported to the DSMB by frequency, severity, relatedness, and (partially blinded) treatment group in closed session DSMB reports. The semi-annual DSMB report will include finalized MedWatch 3500 or Health Canada ADRs Reports. Semi-annual reports will only include SAEs reported during that period. A cumulative SAE summary will also be provided.

Because a large number of deaths are expected due to the condition of the study population at entry to the trial, individual reports of unrelated deaths will be aggregated and reported on a timely schedule acceptable to the DSMB.

Appendix A
Example of OpenClinica Automated e-mail Notification of a Preliminary or Updated SAE Report

---

From: PROPPR HDCC
Sent: *(date/time)*
To: John Holcomb, MD, (independent medical monitor), Barbara Tilley, PhD., Jeanette Podbielski, RN, Steven Kosmach, RN

Subject: (*Preliminary or Updated*) SAE Report

A serious adverse event form has been submitted/updated in OpenClinica for a PROPPR Subject.

Study ID #: __ __ __ __ __ __
Description of SAE Event: _____
SAE Start Date: __ __ / __ __ / __ __
SAE End Date: __ __ / __ __ / __ __
Clinical Site PI Evaluation of SAE: (Expected or Unexpected), (Related or Unrelated)

Appendix B – FDA MedWatch 3500A FORM

Form Approved: OMB No. 09 10-029 1, Expires 12/31/11
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (1/09)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of ____

Mfr Report #

UF/Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   - ☐ Death: _____ *(mm/dd/yyyy)*
   - ☐ Life-threatening
   - ☐ Hospitalization - initial or prolonged
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
   - ☐ Disability or Permanent Damage
   - ☐ Congenital Anomaly/Birth Defect
   - ☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*

4. Date of This Report *(mm/dd/yyyy)*

5. Describe Event or Problem

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. Name *(Give labeled strength & mfr/labeler)*
   #1
   #2

2. Dose, Frequency & Route Used
   #1
   #2

3. Therapy Dates *(If unknown, give duration) from/to (or best estimate)*
   #1
   #2

4. Diagnosis for Use *(Indication)*
   #1
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
   #1
   #2

7. Exp. Date
   #1
   #2

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# or Unique ID

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date *(mm/dd/yyyy)* / Serial # / Other #
5. Operator of Device
   - ☐ Health Professional
   - ☐ Lay User/Patient
   - ☐ Other: _____
6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)*
    ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. INITIAL REPORTER

1. Name and Address
   Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

MEDWATCH

FORM FDA 3500A (1/09) *(continued)* Page 2 of ____

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. **Check One** ☐ User Facility ☐ Importer
2. **UF/Importer Report Number**
3. **User Facility or Importer Name/Address**
4. **Contact Person**
5. **Phone Number**
6. **Date User Facility or Importer Became Aware of Event** *(mm/dd/yyyy)*
7. **Type of Report** ☐ Initial ☐ Follow-up # ____
8. **Date of This Report** *(mm/dd/yyyy)*
9. **Approximate Age of Device**
10. **Event Problem Codes** *(Refer to coding manual)* Patient Code ____ - ____ - ____ Device Code ____ - ____ - ____
11. **Report Sent to FDA?** ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
12. **Location Where Event Occurred** ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: ____ *(Specify)*
13. **Report Sent to Manufacturer?** ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
14. **Manufacturer Name/Address**

G. ALL MANUFACTURERS

1. **Contact Office - Name/Address** ***(and Manufacturing Site for Devices)***
2. **Phone Number**
3. **Report Source** *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ____
4. **Date Received by Manufacturer** *(mm/dd/yyyy)*
5. (A)NDA # ____ IND # ____ STN # ____ PMA/510(k) # ____ Combination Product ☐ Yes Pre-1938 ☐ Yes OTC Product ☐ Yes
6. **If IND, Give Protocol #**
7. **Type of Report** *(Check all that apply)* ☐ 5-day ☐ 30-day ☐ 7-day ☐ Periodic ☐ 10-day ☐ Initial ☐ 15-day ☐ Follow-up # ____
8. **Adverse Event Term(s)**
9. **Manufacturer Report Number**

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: ____
2. **If Follow-up, What Type?** ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. **Device Evaluated by Manufacturer?** ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code: ____
4. **Device Manufacture Date** *(mm/yyyy)*
5. **Labeled for Single Use?** ☐ Yes ☐ No
6. **Evaluation Codes** *(Refer to coding manual)* Method ____ - ____ - ____ - ____ Results ____ - ____ - ____ - ____ Conclusions ____ - ____ - ____ - ____
7. **If Remedial Action Initiated, Check Type** ☐ Recall ☐ Notification ☐ Repair ☐ Inspection ☐ Replace ☐ Patient Monitoring ☐ Relabeling ☐ Modification/Adjustment ☐ Other: ____
8. **Usage of Device** ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. **If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:**
10. ☐ **Additional Manufacturer Narrative** and / or 11. ☐ **Corrected Data**

The public reporting burden for this collection of information has been estimated to average 66 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

OMB Statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Appendix C
Health Canada ADRs Forms

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Health Canada / Santé Canada

Adverse Drug Reactions (ADRs) for Clinical Trials
Expedited Reporting Summary Form

Drug Code, Generic, or Brand Name:

Sponsor of Clinical Trial:

(CR) File Number:

Report Submitted By:

Contact Name and Telephone Number:

Protocol Title / Protocol Number (if applicable):

Sponsor's Identification Number for the case:

Date of ADR Onset:

☐ **Fatal or Life-Threatening Unexpected ADR**

☐ **All other serious and unexpected ADRs**

Is there an ongoing clinical trial for this drug in Canada?

Yes ☐ **No** ☐

FOR DETAILED INFORMATION ON ADVERSE DRUG REACTIONS SUBJECT TO EXPEDITED REPORTING REFER TO PART C DIVISION 5 OF THE FOOD AND DRUG REGULATIONS AND E2A 'CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING' HC / ICH GUIDELINES, 1995

Is this a follow-up to a previous report?

Yes ☐ **No** ☐

If yes , date of previous report (s):

Reported ADR occured in:

☐ **Phase I - III study**

☐ **Phase IV study**

☐ **Spontaneous ADR**

ADR Country of Origin

☐ **Canada**

☐ **Other**

Has the drug been or is it currently marketed in Canada? If yes, provide DIN.

DIN:

Has the drug ever been released under the Special Access Programme/ Emergency Drug Release? **Yes** ☐ **No** ☐

Is there a clinical trial application for this drug under review in Canada? **Yes** ☐ **No** ☐

Is there a new drug submission for this drug under review in Canada? **Yes** ☐ **No** ☐

ADR Reports must be provided by the following deadlines:

Fatal and Life Threatening Unexpected ADRs

1. Initial Report within 7 calendar days
2. Comprehensive Report within an additional 8 calendar days

All Other Serious and Unexpected ADRs

1. Comprehensive Report within 15 calendar days

Signature:

Date:

Appendix D
Sample Cover Letter to FDA

Date:

To: Food and Drug Administration
Attention: *(Agency Representative)*
Center for Biologics Evaluation and Research
WOCI, Room 225N
1401 Rockville Pike
Rockville, MD 20852-1448

IND # XXXXX
Serial # XXXX
IND Safety Report

Dear (name of Agency Representative):

Please refer to the Investigational New Drug Application (IND) **#** XXXXX for our protocol: ***Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)***

The IND holder for IND XXXXX; The University of Texas-Health Science Center respectfully submits our Amendment XXXX, an IND Safety Report for a serious adverse event experienced by patient ID #XX-XXXX-XX ABCDEF. There are *<X number of>* previous safety reports on file with the Agency regarding this or similar events. *<If there are, state this and give amendment number for reference>*

The event, *<diagnosis>*, was *<indicated expected or unexpected>*, *<indicate relationship to study product and/or procedure>*, and *<indicate outcome (if known)*. *<If the event involves a death, even one that is unrelated to study product and/or procedure, include the following statement>* "While the report does not meet the criteria for SAE reporting due to the expected nature of the event, we wish to make the FDA aware of the occurrence of these events. This event has also been reported to the NHLBI-appointed DSMB".

All information included in this IND and all information contained therein is considered **CONFIDENTIAL AND PROPRIETARY** and shall not be released to any other parties without the expressed written consent of the PROPPR Houston Clinical Coordinating Center. The legal protection of such confidential material is hereby claimed under applicable provisions of 21 CFR 312.130.

If you have any questions or require additional information, please contact me at <phone number> and <email address>

Sincerely,

(PI's Name and Credentials)
(IND Sponsor's Authorized Representative)
UTHealth

Cc: Health Canada, NHLBI, DSMB, Independent Medical Monitor, Clinical Site PIs

END OF DOCUMENT

Appendix E
Sample Cover Letter to Health Canada

Date:

To: Blood Establishment Regulation Unit
Attention: *(Agency Representative)*
Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Canada
200 Tunney's Pasture Driveway,
Address Locator 0701A, Tunney's Pasture,
Ottawa, Ontario, K1A 0K9

CTA # 14929
Serial # XXXX
CTA Safety Report

Dear (name of Agency Representative):

Please refer to the Clinical Trial Application (CTA) # 14929 for our protocol: ***Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)***

The IND holder for IND XXXXX; The University of Texas-Health Science Center respectfully submits our Amendment XXXX, an CTA Safety Report for a serious adverse event experienced by patient ID #XX-XXXX-XX ABCDEF. There are *<X number of>* previous safety reports on file with the Agency regarding this or similar events. *<If there are, state this and give amendment number for reference>*

The event, *<diagnosis>*, was *<indicated expected or unexpected>*, *<indicate relationship to study product and/or procedure>*, and *<indicate outcome (if known)*. *<If the event involves a death, even one that is unrelated to study product and/or procedure, include the following statement>* "While the report does not meet the criteria for SAE reporting due to the expected nature of the event, we wish to make Health Canada aware of the occurrence of these events. This event has also been reported to the NHLBI-appointed DSMB".

All information included in this CTA and all information contained therein is considered **CONFIDENTIAL AND PROPRIETARY** and shall not be released to any other parties without the expressed written consent of the PROPPR Houston Clinical Coordinating Center. The legal protection of such confidential material is hereby claimed under applicable provisions of 21 CFR 312.130.

If you have any questions or require additional information, please contact me at <phone number> and <email address>

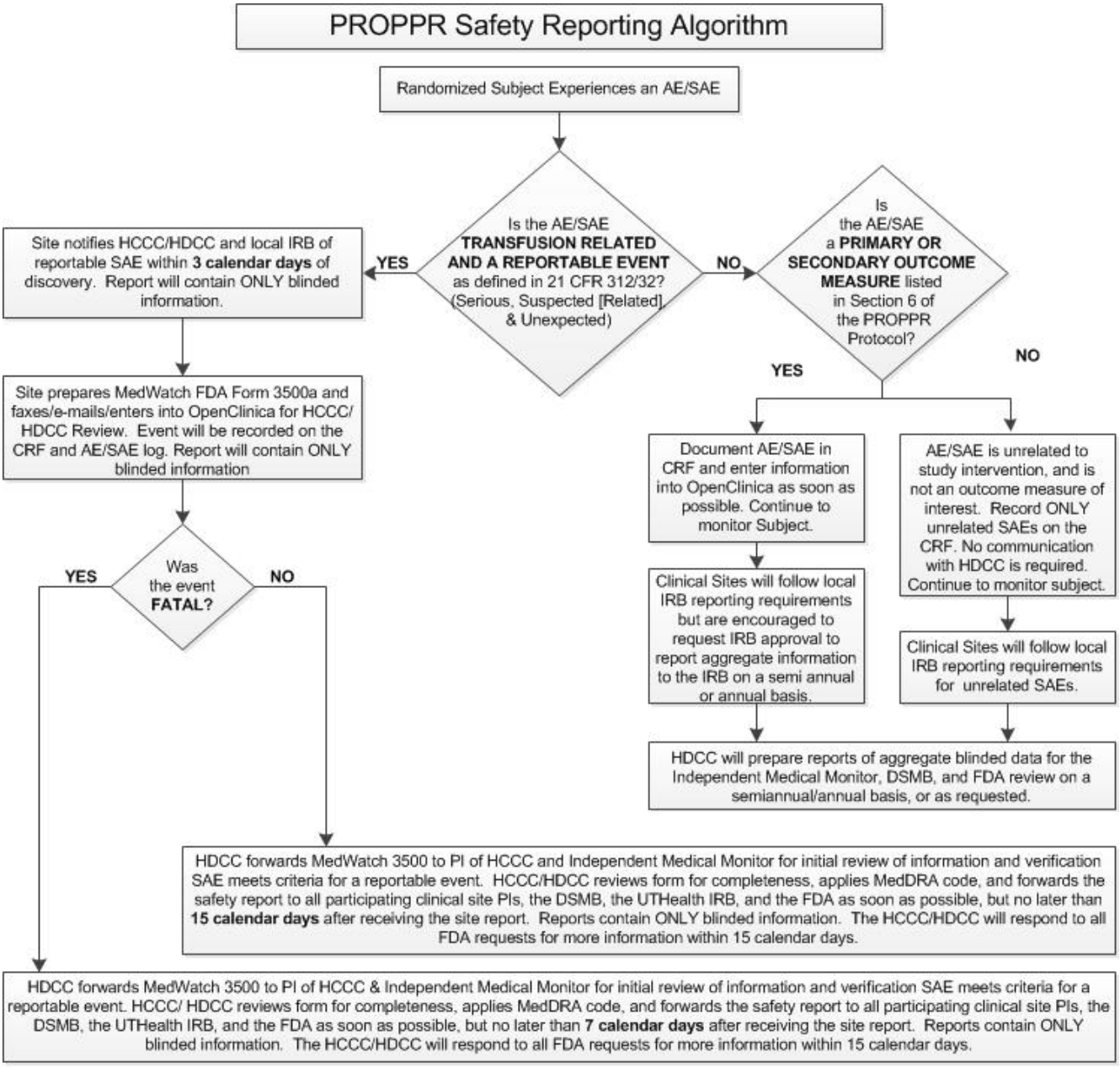
Sincerely,

(PI's Name and Credentials)
(IND Sponsor's Authorized Representative)
UTHealth

Cc: Health Canada, NHLBI, DSMB, Independent Medical Monitor, Clinical Site PIs

END OF DOCUMENT

Appendix F



Definitions:
Adverse Event (AE): Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study intervention without any judgment about causality.
Reportable Event: Event meets ALL the following FDA reporting requirements: event is suspected (related), serious, and unexpected.
Suspected (Related) Adverse Event: There is a reasonable possibility (causal relationship) between the study intervention and the adverse event.
Serious Adverse Event (SAE): An AE is considered serious if, in the view of the PI or Sponsor, it results in any of the following: Death, a life-threatening adverse event, required hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/ incapacitation, required a medical or surgical intervention to prevent death/disability, or an AE resulting in a congenital anomaly/birth defect.
Unexpected: An AE/SAE not listed in the investigator brochure, or not listed at the specificity or severity that has been observed.

References:
FDA Guidance for Clinical Investigators, Sponsors, and IRBs; Adverse Events Reporting to IRBs – Improving Human Subject Protection. January, 2009.
FDA Guidance for Industry and Investigators; Safety Reporting Requirements for INDs and BA/BE Studies. September, 2010.

A modified version of the reporting algorithm will be developed for Health Canada as needed.

Appendix G

The reporting algorithm will be modified for Health Canada requirements as needed.

Section 12.3 Complication Definitions

PROPPR Complications Definitions

1. Abdominal Compartment Syndrome (ACS)

Elevated intra-abdominal pressure (> 20 cm H2O) requiring the opening of the abdominal cavity with at least one of the following: 1) oliguria (<30cc/hr), 2) diminished cardiac output (< 2.5 L/min/m2), 3) elevated static airway pressures (> 45 cm H2O), or 4) PaO2/FiO2 ratio of less than 200. *(TRDB, 2007)*

2. Acute Hemolytic Transfusion Reactions (AHTR)

Rapid destruction of red blood cells during, immediately after, or within 24 hours of cessation of transfusion. Clinical and laboratory signs of hemolysis are present. No single criterion exists to definitively diagnose this rare disorder.

Definitive: Any of the following: Chills/rigors, Fever, Back/flank pain, Hypotension, Hemoglobinuria occurring during or shortly after cessation of transfusion, Epistaxis, Oliguria/anuria, Renal failure, Disseminated intravascular coagulation (DIC), Pain and/or oozing at IV,

AND EITHER:

(1) ABO incompatibility or other allotypic RBC antigen incompatibility

OR,

(2) Clerical check indicates that the patient's name and blood group on the blood unit are different than the recipient's name and blood group.

Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.

Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.

Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.

Grade 4-Death: Subject died as a result of the adverse transfusion reaction.

(HNSN, 2011)

3. Acute Kidney Injury (AKI) / Acute Renal Failure

Rapid loss of kidney function (within any 48 hours), measured by a rise in creatinine (increase in serum creatinine of either an absolute count of >/= 0.3 mg/dl or 50% increase), decrease in the GFR (> 25%) and/or reduction in urine output defined as <0.5 ml/kg/hr for at least 6 hours.

(Acute Kidney Injury Network, 2007)

4. Acute Lung Injury (ALI)

Lung injury characterized by hypoxemia, pulmonary edema, low lung compliance and capillary leakage. The following 3 criteria must be met within a 24 hour period:

1) Bilateral infiltrates on a CXR (acute onset),

2) PaO2/FiO2≤300 regardless of PEEP,

3) No evidence of left atrial hypertension (PCWP ≤ 18) or no evidence of congestive heart failure in the absence of a PAC. If a PAC is in place there must be evidence that the PCWP was ≤ 18 for at least 12 consecutive hours during the 24 hour assessment block.

(TRDB, 2007)

5. Acute Respiratory Distress Syndrome (ARDS)-

Lung injury characterized by hypoxemia, pulmonary edema, low lung compliance and capillary leakage. The following 3 criteria must be met within a 24 hour period:

1) Bilateral infiltrates on a CXR (acute onset),
2) PaO2/FiO2 ≤ 200 regardless of PEEP,
3) No evidence of left atrial hypertension (PCWP ≤ 18) or no evidence of congestive heart failure in the absence of a PAC. If a PAC is in place there must be evidence that the PCWP was ≤ 18 for at least 12 consecutive hours during the 24 hour assessment block.
(TRDB, 2007)

6. Allergic Reactions (Transfusion Related)

The result of an interaction of an allergen with preformed antibodies. In some instances, infusion of antibodies from an atopic donor may also be involved. It may present with only mucocutaneous signs and symptoms.
Definitive: 2 or more of the following occurring during or within 4 hours of cessation of transfusion: Maculopapular Rash, Urticaria, Pruritus, Generalized Flush, Localized Angioedema, Edema of Lips, Tongue, & Uvula, Erythema & Edema of the Periorbital Area, Conjunctival Edema, Respiratory Distress, Bronchospasm, Hypotension. PROBABLE: Any 1 of the following occurring during or within 4 hours of cessation of transfusion: Maculopapular Rash, Urticaria, Pruritus, Localied Angioedema, Edema of the Lips, Tongue, & Uvula, Erthema& Edema of the Periorbital Area, Conjunctival Edema.
Grade 1: No immediate risk to the life of the patient AND responds quickly to symptomatic treatment.
Grades 2-4: Involves respiratory and/or cardiovascular systems and presents like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous symptoms, there are airway symptoms, hypotension, or associated symptoms like hypotonia and syncope. The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing, bronchospasm, hypoxemia). Such a reaction usually occurs during or shortly after cessation of transfusion.
(HNSN, 2011)

7. Bacteremia

The presence of viable bacteria in the blood with positive blood cultures.
(American College of Chest Physicians/Society of Critical Care Medicine, 1992)

8. Cardiac Arrest

Sudden cessation of cardiac activity (Includes pulseless electrical activity [PEA]).
(TRDB, 2007)

9. Catheter-Related Bloodstream Infections (CRBSI)

The presence of bacteremia/fungemia in a patient with a central venous catheter (CVC) in which there is no alternate source for bacteremia/fungemia except the catheter. To diagnose CRBSI, the patient must have clinical manifestations of infection (fever, chills or hypotension); a positive blood culture from a peripheral vein; and some microbiologic evidence the catheter is infected.
Diagnostic criteria (all of 1, 2 and 3 must be met within a 48 hr period):
1. A single positive blood culture from a peripheral vein
2. Clinical manifestations of infection including at least one of a, b, or c
    a) Fever >38.5C
    b) WBC >10,000 or < 3000 per cubic millimeter
    c) Hypotension (SBP < 90) or > 25% drop in systolic blood pressure

3. Microbiologic evidence of catheter infection (at least one of a, b, c, or d)
    a) positive semiquantitative (>15CFU/catheter segment) culture in which the same organisms isolated from the catheter and peripheral blood (**this is the most commonly used technique)**
    b) positive quantitative (>103CFU/catheter segment catheter) culture in which the same organism is isolated from the catheter and peripheral blood
    c) simultaneous quantitative blood cultures with a ≥ 5:1ratio of bacteria (CVC versus

peripheral)

d) differential period of central venous catheter culture versus peripheral blood culture positivity of > 2 hours*(TRDB, 2007)*

10. Delayed Hemolytic Transfusion Reactions (DHTR)

The recipient develops antibodies to RBC antigen(s) between 24 hours and 28 days after cessation of transfusion. Clinical signs of hemolysis are usually present. If performed, post-transfusion LDH and bilirubin levels increase and subsequently fall back to baseline in the following days. Patient may be asymptomatic or have symptoms that are similar to but milder than AHTR. Examples of symptoms include: Chills/Rigors, Fever, Jaundice, Back/Flank Pain, Hypotension, Hemoglobinuria/Hematuria, Oliguria/Anuria. **NOTE:** These symptoms are **NOT** required to meet definitive case criteria.

Definitive:

Positive direct antiglobulin test (DAT) for antibodies developed between 24 hours and 28 days after cessation of transfusion.

AND EITHER

- Positive elution test with alloantibody present on the transfused red blood cells

OR

- Newly-identified red blood cell alloantibody in recipient serum

AND EITHER

- Inadequate rise of post-transfusion hemoglobin level or rapid fall in hemoglobin back to pre-transfusion levels

OR

- Otherwise unexplained appearance of spherocytes.

Probable:

Newly-identified red blood cell alloantibody demonstrated between 24 hours and 28 days after cessation of transfusion **BUT n**ot enough laboratory evidence to meet definitive criteria.

Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.

Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.

Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.

Grade 4-Death: Subject died as a result of the adverse transfusion reaction.

(HNSN, 2011)

11. Delayed Serological Transfusion Reactions (DSTR)

Demonstration of new, clinically-significant antibodies against red blood cells between 24 hours and 28 days after cessation of a transfusion despite an adequate, maintained hemoglobin response.

Definitive:

Demonstration of new, clinically-significant antibodies against red blood cells between 24 hours and 28 days after cessation of a transfusion that were not present in the pre-transfusion specimen

BY EITHER

- Positive direct antiglobulin test (DAT)

OR

- Positive antibody screen with newly identified RBC alloantibody.

Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.

Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the

adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.
Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.
Grade 4-Death: Subject died as a result of the adverse transfusion reaction.
(HNSN, 2011)

12. Febrile Non-hemolytic Transfusion Reaction (FNHTR)

Fever and/or chills **without** hemolysis occurring in the patient during or within 4 hours of cessation of transfusion. If transfusion-related, the most common cause is a reaction to passively transfused cytokines or a reaction of recipient antibodies and leukocytes in the blood product. If blood culture of patient or residual component is performed, the results should be negative. Laboratory findings should show no evidence of acute hemolysis.
Definitive: Occurs during or within 4 hours of cessation of transfusion
AND EITHER

- Fever (greater than or equal to 38oC oral or equivalent and a change of at least 1^{o}C from pre-transfusion value)

OR

- Chills/rigors are present.

Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.
Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.
Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.
Grade 4-Death: Subject died as a result of the adverse transfusion reaction.
(HNSN, 2011)

13. Hyperkalemia within 24 hours of admission (transfusion-related)

Potassium levels ≥ 6mEq/L without preexisting chronic renal failure.

14. Hypernatremia

Serum sodium level > 165mEq/L.

15. Hypocalcemia within 24 hours of admission (transfusion-related)

Ionized Calcium levels ≤ 1.0 mg/dL or 4.0 mg/dL.

16. Hypotensive Transfusion Reaction

A drop in blood pressure occurring during or within one hour of cessation of transfusion not associated with hypovolemia. Other symptoms, such as facial flushing, dyspnea, or abdominal cramps may occur but usually hypotension is the sole manifestation.
Definitive: ALL OF THE FOLLOWING:

- Hypotension: Drop in systolic BP of greater than or equal to 30 mmHg **AND** Systolic BP less than or equal to 80 mmHg.
- Occurs less than 15 minutes after the start of the transfusion.
- Responds rapidly (within 10 minutes) to cessation of transfusion and supportive treatment.
- All other adverse reactions presenting with hypotension must be excluded.

Grade 1: The recipient required no more than discontinuation of transfusion and symptom management AND no long-term morbidity resulted from the reaction.
Grade 2: The recipient required in-patient hospitalization or prolongation of hospitalization due to hypotension or hypotension led directly to long-term morbidity (e.g., brain damage) AND vasopressors were not required.
Grade 3: The recipient required vasopressors.
Grade 4: The recipient died as a result of the hypotensive transfusion reaction or as a result of treatment directly related to resolving symptoms of the reaction.
(HNSN, 2011)

17. Multiple Organ Failure (MOF)

Multiple organ failure will be defined using the Denver Multiple Organ Failure (MOF) scoring system. This system evaluates four organ systems: pulmonary, hepatic, renal, and cardiac. Organ dysfunction is graded on a scale from 0 to

The pulmonary score is determined by the PaO2/FiO2 (P/F) ratio. P/F >208 receive zero (0) points, ratios of 208-165 receive 1 point, 165-83 receive 2 points, and 83 receive 3 points.

The renal system is graded by serum creatinine level in mg/dL: 0 points for <1.8, 1 point for 1.8-2.5, 2 points for 2.5-5.0, and 3 points for >5.0 mg/dL.

The hepatic score is calculated by total serum bilirubin level in mg/dL: 0 points for bilirubin <2.0, 1 point for 2.0-4.0, 2 points for 4.0-8.0, and 3 points for bilirubin >8.0 mg/dL.

Cardiac dysfunction is graded based on inotropic support and cardiac index (C.I.). No inotropes and cardiac index >3.0 L/min per meter squared yield a score of zero (0), whereas minimal inotropic support or C.I. <3.0 yield a score of 1. Moderate and high dose inotropic receive scores of 2 and 3, respectively.

Scores not recorded are assumed to be normal and calculated as zero (0).

****For multiple organ failure, the MOF score is calculated as the sum of the simultaneously obtained individual organ scores on each hospital day. Single system organ failure is defined as an organ failure grade >0. MOF is defined as a total score of 4 or greater.

18. Post Transfusion Purpura (PTP)

Thrombocytopenia usually arising 5-12 days following transfusion of cellular blood components with findings of antibodies in the patient directed against the Human Platelet Antigen (HPA) system.
Definitive: Thrombocytopenia (decrease to less than 20% of pre-transfusion count).
Alloantibodies in the patient directed against HPA-1a or other platelet specific antigen detected at or after development of reaction.
Probable: Drop in platelets to levels between 20% and 80% of pre-transfusion count.
Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.
Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.
Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.
Grade 4-Death: Subject died as a result of the adverse transfusion reaction.
(HNSN, 2011)

19. Sepsis

A systemic response to infection. Two or more of the following three conditions must be present: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaC02<32 mmHg; and white blood cell count >12,000/cu mm,<4,000/cu mm, or> 10% immature (band) forms; AND a known or suspected infection confirmed by culture, CXR, or CT. *(American College of Chest Physicians/Society of Critical Care Medicine, 1992)*

20. Systemic Inflammatory Response Syndrome (SIRS)

SIRS is a serious condition related to systemic inflammation, organ dysfunction, and organ failure. It is a subset of cytokine storm, in which there is abnormal regulation of various cytokines. Two or more of the following must be present for SIRS (without a positive culture): 1) temperature below 36^{o} C or above 38^{o} C, 2) heart rate > 90 bpm, 3) > 20 breaths per minute or, on blood gas, a PaCO2 less than 32 mmHg, 4) WBC < 4,000 cells/mm3 or > 12,000 cells/mm3. *(American College of Chest Physicians/Society of Critical Care Medicine, 1992)*

21. Surgical Site Infections (SSI)

Superficial Incisional/Wound Infections

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision **and at least one** of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

(TRDB, 2007)

Deep Incisional SSI

Infection occurs within 30 days after the operation and the infection appears to be related to the operation*and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision ***and*** at least ***one*** of the following:

1. Purulent drainage from the deep incision, but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC), localized pain or tenderness, unless site is culture-negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Organ/Space SSI

Infection occurs within 30 days after the operationand the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation ***and*** at least ***one*** of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space (if the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.)
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

(TRDB, 2007)

22. Thromboembolic complications

a. **Myocardial Infarction (MI)**

Acute, irreversible myocardial injury documented by both of: (1) Abnormal increase in CK-MB ortroponin and (2) New, serial T-wave, S-T segment or Q wave ECG abnormalities. *(TRDB, 2007*

b. **Stroke or Cerebral Infarction.** New neurological deficit not present on admission which is: 1) sudden or rapid in onset, 2)and lasts >24 hours and 3) confirmed as an acute infarction by CT or MRIand 4) that is consistent with the physical exam. *(TRDB, 2007)*

c. **Deep Vein Thrombosis (DVT)** – venous thrombosis confirmed by autopsy, venogram, duplex or other non-invasive vascular evaluation. Document whether the DVT is symptomatic or not

d. **Pulmonary Embolus (PE)** A clinically significant (resulting in hypoxia or tachycardia or hypotension) blood clot lodged in the lumen of a pulmonary artery as diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan. To be differentiated from occult, non-clinically significant PE. *(ROC Hypertonic Resuscitation MOO, 2008)*

e. **Mesenteric Thrombosis** (arterial or venous) Documented on arteriogram, CT angiogram, operative findings or autopsy

f. **Other (not superficial vein thrombi)**

23. Transfusion-Associated Circulatory Overload (TACO)

Infusion volume that cannot be effectively processed by the recipient either due to high rate and/or volume of infusion or an underlying cardiac or pulmonary pathology

Definitive: New onset or exacerbation of 3 or more of the following within 6 hours of cessation of transfusion:

- Acute onset of respiratory distress symptoms (dyspnea, orthopnea, cough),
- Evidence of positive fluid balance,
- Elevated brain natriuretic peptide (BNP),
- Radiographic evidence of pulmonary edema,
- Evidence of left heart failure,
- Elevated central venous pressure (CVP)

Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.

Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.

Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.

Grade 4-Death: Subject died as a result of the adverse transfusion reaction.

(HNSN, 2011)

24. Transfusion-Associated Dyspnea (TAD)

Respiratory distress within 24 hours of cessation of transfusion *that does not meet the criteria of TRALI, TACO, or allergic reaction.* Respiratory distress should not otherwise be explained by a patient's underlying or pre-existing medical condition.

Definitive: Acute respiratory distress occurring within 24 hours of cessation of transfusion AND TRALI, TACO, and allergic reactions are ruled out.

Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.

Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of

a body function.
Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.
Grade 4-Death: Subject died as a result of the adverse transfusion reaction.
(HNSN, 2011)

25. Transfusion-Associated Graft vs. Host Disease (TAGVHD)

The introduction of immunocompetent lymphocytes into susceptible hosts. The allogeneic lymphocytes engraft, proliferate and destroy host cells. If performed, marrow study shows hypoplasia, aplastic anemia, or marked hypocellularity with a lymphohistiocytic infiltrate.
Definitive: A clinical syndrome occurring from 2 days to 6 weeks after cessation of transfusion characterized by:

- Fever;
- Characteristic rash: erythematous, maculopapular erupting centrally and spreading to extremities, in severe cases may progress to generalized erythroderma and hemorrhagic bullous formation;
- Hepatomegaly;
- Diarrhea.

Grade 1: N/A
Grade 2: Patient had marked symptoms and responded to treatment.
Grade 3: Patient had severe symptoms and required life-saving treatment (e.g., immunosuppression).
Grade 4: Patient died from TAGVHD.
(HNSN, 2011)

26. Transfusion-Related Acute Lung Injury (TRALI)

Acute hypoxemia with PaO2/fraction of inspired oxygen [FIO2] ratio of <300 mmHg combined with chest x-ray showing bilateral infiltrates in the absence of left atrial hypertension (i.e., circulatory overload). Onset of TRALI is abrupt in association with transfusion. Must be discussed with and corroborated with head of the blood bank based on local standard blood bank policy.
Definitive: No evidence of acute lung injury (ALI) prior to transfusion **AND** ALI onset during or within 6 hours of cessation of transfusion **AND** Hypoxemia defined by any of these methods: PaO2 / FiO2< 300 mm Hg; Oxygen saturation less than 90% on room air; other objective evidence **AND** no evidence of left atrial hypertension (i.e. circulatory overload).
Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function.
Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.
Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.
Grade 4-Death: Subject died as a result of the adverse transfusion reaction.
(HNSN, 2011)

27. Transfusion-Related Metabolic Complication (Hypocalcemia/Hyperkalemia)

Metabolic complications may accompany large-volume transfusions, especially in neonates and patients with liver or kidney disease.

a. Citrate "toxicity" reflects a depression of ionized calcium caused by the presence in the circulation of large quantities of citrate anticoagulant. Because citrate is promptly metabolized by the liver, this complication is rare. Patients with severe liver disease or those with circulatory collapse that prevents adequate hepatic blood flow may have physiologically significant hypocalcemia after rapid, large-volume transfusion. Citrated blood or blood components administered rapidly through central

intravenous access may reach the heart so rapidly that ventricular arrhythmias occur. Standard measurement of serum calcium does not distinguish ionized from complexed calcium. Ionized calcium testing or electrocardiogram monitoring is more helpful in detecting physiologically significant alteration in calcium levels.

b. Other metabolic derangements can accompany rapid or large-volume transfusions, especially in patients with preexisting circulatory or metabolic problems. These include acidosis or alkalosis (deriving from changing concentrations of citric acid and its subsequent conversion to pyruvate and bicarbonate) and hyperkalemia- or hypocalcemia.
c. Hypocalcemia/Hyperkalemia resulting in an arrythemia resulting in focused electrolyte therapy.

(AABB Circular of Information, 2009)

28. Transfusion-Transmitted Infection

A bacteria, parasite, virus, or other potential pathogen transmitted in donated blood to transfusion recipient. Refer to CDC/NHSN Biovigilance Component Manualfor detailed information.
Grade 1-Non-Severe: Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. Grade 2-Severe: Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.
Grade 3-Life Threatening: Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death.
Grade 4-Death: Subject died as a result of the adverse transfusion reaction.
(HNSN, 2011)

29. Ventilator Associated Pneumonia (VAP)

Pneumonia in patients who have been mechanically ventilated for < 48 hours.
Criteria a-c must be satisfied within a 48 hr period:

a) Radiologic criteria:
i. New radiographic infiltrate that persists for at least 24 hours not associated with ALI, ARDS, pulmonary contusion, TRALI or TACO.
b) Clinical criteria (one of i or ii)
i. Tm> 38.5°C or <35.0°C
ii. WBC> 12,000 or <4000 per cubic millimeter
c) Bacterial confirmation by at least one of:
i. Quantitative microbiologic cultures obtained by bronchoalveolar lavage yielding≥10^4colony forming units [CFU]/ml or protected specimen brush>10^3 CFU/ml (preferred diagnostic method)
ii. Histopathologic exam of lung tissue shows one of a or b:
(a). Abscess formation with intense PMN accumulation in bronchioles &alveoli. (b). Quantitative culture of lung parenchyma that shows ≥ 10^4cfu/g tissue.
iii. Positive blood culture for bacterial pathogen identified in sputum or respiratory culture
iv. Positive pleural fluid culture with same organism identified in sputum or other respiratory cultures
v. Positive sputum gram stain with ≥3+ of one type of pathogenic bacteria
vi. Heavy or moderate growth of one type of pathogenic bacteria on semi-quantitativesputum culture

(TRDB, 2007)

30. Abdominal Complications (Open or Closed) after Exploratory Laparotomy

Abdominal complications include:

a. Fistula – abnormal connection between two epithelial-lined organs that normally do not connect.

b. Abscess of other evidence of any infection involving the intra-abdominal or retroperitoneal contents is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
c. Other (please specify)

31. Other, please describe

References

Bone, R.; Balk, R.; Cerra, F.; Dellinger, R.; Fein, A.; Knaus, W.; Schein, R.; Sibbald, W. (1992)."Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine".*Chest***101** (6): 1644–55. doi:10.1378/chest.101.6.1644. PMID1303622

Circular of Information for the use of Human Blood and Blood Components. AABB, American Red Cross, America's Blood Centers, and the Armed Services Blood Program. December, 2009.

Infections and Non-Infectious Complications – Definitions from the Trauma-Related Database (TRDB). 10/22/2007.

Mehta RL, Kellum JA, Shah SV, *et al.* (2007). "Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury". *Critical Care (London, England)***11** (2): R31. doi:10.1186/cc5713. PMC2206446.PMID17331245

The National Healthcare Safety Network (NHSN) Manual. Biovigilance Component. Division of Healthcare Quality Promotion, Nation Center for Emerging and Zoonotic Infectious Diseases, and the Center for Disease Control and Prevention.Protocol v1.3.1. June 2011. www.cdc.gov/nhsn

Section 12.4 Instructions for Completing CRF Form #18: AE/SAE's

Complete this form to record AE/SAE's on randomized subjects from ED admission through discharge or day 30. Complete this form for all randomized subjects. Record only the AE/SAE's listed on the form using the codes provided. Refer to the PROPPR safety monitor plan for specific information on AE/SAE reporting requirements. Record the start and stop dates of the AE/SAE in dd/mmm/yy format or select "ongoing" or "unknown" for the stop date if applicable. If the end date is known, the status should be left blank. Indicate if the AE/SAE was expected for the subject given their unique trauma injuries and comorbidities. Indicate if the AE/SAE was suspected (related) to receiving randomized PROPPR MT blood products. Select the seriousness of the AE/SAE using criteria from the PROPPR Complications Definitions document.

Hypertonic saline associated hypernatremia and transfusion related graft vs. host disease should be reported to the HDCC within 3 calendar days of discovery and require expedited FDA reporting. Refer to the PROPPR Safety and Monitoring Plan in Section 12.2. for more detailed information.

Report all deaths prior to discharge or day 30 to the HDCC. Refer to Section 12.7 for more information on death adjudication.

Please note form # 18 is designed to meet regulatory AE/SAE reporting requirements. "Severe" is often used to describe the intensity of an event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). The criterion is NOT the same as "serious" which is based on a subject event/outcome or medical/surgical interventions required to treat the event posing a threat to the subject's life or functioning.

Seriousness, not severity, serves as a guide for regulatory reporting.

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012AUG27 Completed By: ___ ___ ___

Form 18: Adverse Events & Serious Adverse Events (AEs, SAEs)

Check here ☐ if there are NO AE/SAE events to report.

(Record any of the following complications that occurred during the subject's initial hospitalization. ****** *Hypertonic saline associated hypernatremia and transfusion associated graft vs. host disease should be reported to the HDCC within 3 days of discovery for FDA expedited reporting. Print additional pages as needed.)*

CODE	AE / SAE	CODE	AE / SAE	CODE	AE / SAE
1	Abdominal Compartment Syndrome (ACS)	13	Myocardial Infarction (MI)	25	Delayed Hemolytic Transfusion Reaction (DHTR)
2	Acute Kidney Injury	14	Open Abdominal Complication	26	Delayed Serological Transfusion Reaction (DSTR)
3	Acute Lung Injury	15	Other: (specify)	27	Febrile Non-Hemolytic Transfusion Reaction
4	Acute Respiratory Distress Syndrome (ARDS)	16	Pulmonary Embolism (PE), Symptomatic	28	Hypotensive Transfusion Reaction
5	Cardiac Arrest	17	Pulmonary Embolism (PE), Asymptomatic	29	Post Transfusion Purpura (PTP)
6	Death-NOT Transfusion Related	18	Re-Bleeding **After** Hemostasis Requiring I.R. / O.R. Procedure	30	Transfusion Associated Circulatory Overload (TACO)
7	Deep Vein Thrombosis (DVT)	19	Renal Failure	31	Transfusion Associated Dyspnea (TAD)
8	Drug Reaction	20	Sepsis	****32****	**Transfusion Associated Graft vs. Host Disease (TAGVHD)**
****9****	**Hypernatremia (associated with hypertonic saline)**	21	Stroke	33	Transfusion Related Acute Lung Injury (TRALI)
10	Infection (UTI, Wound, Line, etc.)	22	Systemic Inflammatory Response Syndrome (SIRS)	34	Transfusion Related Allergic Reactions
11	Mesenteric Thrombosis	23	Ventilator Associated Pneumonia (VAP)	35	Transfusion Related Metabolic Complication (Hypo/Hypercalemia)
12	Multiple Organ Failure (MOF)	24	Acute Hemolytic Transfusion Reaction (AHTR)	36	Transfusion Transmitted Infection

↓

Code	AE / SAE	Start Date (dd/mmm/yy)	Stop Date (dd/mmm/yy)		Expected? (For Trauma Injuries)	Suspected? (Related to Randomized Blood Products)	Serious?
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death
	☐ AE ☐ SAE	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 Non-Serious ☐ 2 Serious ☐ 3 Death

Refer to "Definitions of Complications Reported in PROPPR" reference for more information.

Site P.I. Name: Signature:

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of ____

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. **Patient Identifier** In confidence
2. **Age at Time of Event or Date of Birth:**
3. **Sex** ☐ Female ☐ Male
4. **Weight** _____ lb or _____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)* ☐ Disability or Permanent Damage
☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. **Date of Event** *(mm/dd/yyyy)*
4. **Date of this Report** *(mm/dd/yyyy)*

5. **Describe Event, Problem or Product Use Error**

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1 Name:
Strength:
Manufacturer:
#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1		
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2. **Common Device Name**
3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mm/dd/yyyy)*
7. **If Explanted, Give Date** *(mm/dd/yyyy)*
8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?** ☐ Yes ☐ No
9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
Name:
Address:
City: State: ZIP:

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: http://www.fda.gov/medwatch/report/consumer/instruct.htm

Report adverse events, product problems or product use errors with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Combination products *(medication & medical devices)*
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

-Fold Here-

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- www.fda.gov/medwatch/report.htm - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

-Fold Here-

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

The public reporting burden for this collection of information has been estimated to average 36 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (1/09) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

(CONTINUATION PAGE)

For VOLUNTARY reporting of adverse events and product problems

Page 3 of ____

B.5. **Describe Event or Problem** *(continued)*

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

F. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (continued)*

General Instructions for Completing the MedWatch Form FDA 3500

For use by health professionals and consumers for **VOLUNTARY** reporting of adverse events, product use errors and product quality problems with:

- Drugs
- Biologics (including blood components, blood derivatives, allergenics, human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- Medical devices (including *in-vitro* diagnostics)
- Combination products (e.g. drug-device, biologic-device)
- Special nutritional products (dietary supplements, infant formulas, medical foods)
- Cosmetics

Adverse events involving **vaccines** should be reported to the Vaccine Adverse Event Reporting System (VAERS), http://vaers.hhs.gov/pdf/vaers_form.pdf Adverse events involving **investigational (study) drugs, such as those relating to Investigational New Drug (IND) applications**, should be reported as required in the study protocol and sent to the address and contact person listed in the study protocol. They should generally not be submitted to FDA MedWatch as voluntary reports.

Note for consumers: If possible, please take the 3500 form to your health professional (e.g., doctor or pharmacist) so that information based on your medical record that can help in the evaluation of your report will be provided. If, for whatever reason, you do not wish to have your health professional fill out the form, you are welcome to do so yourself.

GENERAL INSTRUCTIONS

- Please make sure that all entries are either typed, printed in a font no smaller than 8 point, or written using black ink.
- Please complete all sections that apply to your report.
- Dates should be entered as mm/dd/yyyy (e.g., June 3, 2005 = 06/03/2005). If exact dates are unknown, please provide the best estimate (see block **B3**).
- For narrative entries, if the fields do not provide adequate space, attach additional pages as needed.
- If attaching additional pages, please do the following:
  - Identify all attached pages as Page __ of __
  - Indicate the appropriate section and block number next to the narrative continuation.
  - Include the phrase continued at the end of each field that has additional information continued on to another page.
- **Section D,** Suspect product(s), should be used to report on special nutritional products and cosmetics as well as drugs or biologics, including human cells, tissues, and cellular and tissue-based products (HCT/Ps).
- If your report involves a serious adverse event with a device and it occurred in a facility other than a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

SECTION A: PATIENT INFORMATION

Complete a separate form for each patient, unless the report involves a medical device where multiple patients were adversely affected through the use of the same device. In that case, please indicate the number of patients in block **B5** (Describe event or problem) and complete Section A and blocks **B2**, **B5**, **B6**, **B7**, and **F** for each patient. Enter the corresponding patient identifier in block **A1** for each patient involved in the event.

Parent-child/fetus report(s) are those cases in which either a fetus/breast-feeding infant or the mother, or both have an adverse event that is possibly associated with a product administered to the mother during pregnancy. Several general principles are used for filing these reports:

- If there has been no event affecting the child/fetus, report only on the parent.
- For those cases describing fetal death, miscarriage or abortion, report the parent as the patient in the report.
- When only the child/fetus has an adverse reaction/ event (other than fetal death, miscarriage or abortion), the information provided in **Section A** applies to the child/fetus. However, the information in **Section D** would apply to the parent who was the source of exposure to the product.
- When a newborn baby is found to have a birth defect/congenital anomaly that the initial reporter considers possibly associated with a product administered to the mother during pregnancy, the patient is the newborn baby.
- If both the parent and the child/fetus have adverse events, separate reports should be submitted for each patient.

A1: Patient Identifier

Please provide the patient's initials or some other type of identifier that will allow you, the reporter, to readily locate the case if you are contacted for more information. Do not use the patient's name or social security number.

The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

If no patient was involved (such as may be the case with a product problem), enter none.

A2: Age at Time of Event or Date of Birth

Provide the most precise information available. Enter the patient's birth date, if known, or the patient's age at the time of event onset. For age, indicate time units used (e.g., years, months, days):

- If the patient is 3 years or older, use years (e.g., 4 years).
- If the patient is less than 3 years old, use month (e.g., 24 months).
- If the patient is less than 1 month old, use days (e.g., 5 days).
- Provide the best estimate if exact age is unknown.

A3: Sex

Enter the patient's gender. If the adverse event is a congenital anomaly/birth defect, report the sex of the child.

A4: Weight

Indicate whether the weight is in pounds (lb) or kilograms (kg). Make a best estimate if exact weight is unknown.

SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR

B1: Adverse Event, Product Problem, Product Use Error, or Problem with Different Manufacturer of Same Medicine.

Choose the appropriate box(es). If a product problem may have caused or contributed to the adverse event, check both boxes.

Adverse event: Any incident where the use of a medication (drug or biologic, including HCT/P), at any dose, a medical device (including *in-vitro* diagnostics) or a special nutritional product (e.g., dietary supplement, infant formula or medical food) is suspected to have resulted in an adverse outcome in a patient.

To report, it is not necessary to be certain of a cause/effect relationship between the adverse event and the use of the medical product(s) in question. Suspicion of an association is sufficient reason to report. Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Please limit your submissions to those events that are serious. An event is classified as serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Medical or Surgical Intervention to Prevent Permanent Impairment or Damage (Devices)
- Other Serious (Important Medical Events)

Please see instructions for block **B2** for further information on each of these criteria.

Product problem (e.g., defects/malfunctions): Any report regarding the quality, performance, or safety of any medication, medical device or special nutritional product. In addition, please select this category when reporting device malfunctions that could lead to a death or serious injury if the malfunction were to recur. Product problems include, but are not limited to, such concerns as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Therapeutic failures (product didn't work)
- Product confusion (caused by name, labeling, design or packaging)
- Suspected superpotent or subpotent medication
- Labeling problems caused by printing errors/omissions

Product Use Error:

Medication Use Error: Any report of a medication error regardless of patient involvement or outcome. Also report circumstances or events that have the capacity to cause error (e.g., similar product appearance, similar packaging and labeling, sound-alike/look-alike names, etc.).

Medication errors can and do originate in all stages of the medication use system, which includes selecting and procuring drugs, prescribing, preparing and dispensing, administering and monitoring. A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use."

Medical Device Use Error: Health care professionals, patients, and consumers can unintentionally cause harm to patients or to themselves when using medical devices. These problems can often arise due to problems with the design of the medical device or the manner in which the device is used. Often, use errors are caught and prevented before they can do harm (close call). Report use errors regardless of patient involvement or outcome. Also report circumstances or events that could cause use errors. Medical device use errors usually occur for one or more of the following reasons:

- Users expect devices to operate differently than they do.
- Product use is inconsistent with use's expectations or intuition.
- Product use requires physical, perceptual, or cognitive abilities that exceed those of the user.
- Devices are used in ways not anticipated by the manufacturer.
- Product labeling or packaging is confusing or inadequate.
- The environment adversely affects or influences device use.

Problem with Different Manufacturer of Same Medicine: Any incident, to include, but not be limited to, differences in noted therapeutic response, suspected to have resulted from a switch, or change, from one manufacturer to another manufacturer of the **same** medicine or drug product. This could be changes from a brand name drug product to a generic manufacturer's same product, or from a generic manufacturer's product to the same

(continued on next page)

SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR *(continued)*

product as supplied by a different generic manufacturer, or from a generic manufacturer's product to a brand name manufacturer of the same product. In order to fully evaluate the incident, please include in **Section B5**, if available, specific information relative to the switch between different manufacturers of the same medicine, to include, but not be limited to, the names of the manufacturers, length of treatment on each manufacturer's product, product strength, and any relevant clinical data.

B2: Outcomes Attributed to Adverse Event: Indicate all that apply to the reported event:

Death: Check ony if you suspect that the death was an outcome of the adverse event, and include the date if known.

Do not check if:

- The patient died while using a medical product, but there was no suspected association between the death and the use of the product
- A fetus is aborted because of a congenital anomaly (birth defect), or is miscarried

Life-threatening: Check if suspected that:

- The patient was at substantial risk of dying at the time of the adverse event, or
- Use or continued use of the device or other medical product might have resulted in the death of the patient

Hospitalization (initial or prolonged): Check if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Do not check if:

- A patient in the hospital received a medical product and subsequently developed an otherwise nonserious adverse event, unless the adverse event prolonged the hospital stay

Do check if:

- A patient is admitted to the hospital for one or more days, even if released on the same day
- An emergency room visit results in admission to the hospital. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious (medically important event)

Disability or Permanent Damage: Check if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions. Such would be the case if the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect: Check if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices): Check if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events): Check when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

B3: Date of Event

Provide the actual or best estimate of the date of first onset of the adverse event. If day is unknown, month and year are acceptable. If day and month are unknown, year is acceptable.

- When a newborn baby is found to have a congenital anomaly, the event onset date is the date of birth of the child.
- When a fetus is aborted because of a congenital anomaly, or is miscarried, the event onset date is the date pregnancy is terminated.
- If information is available as to time during pregnancy when exposure occurred, indicate that information in narrative block **B5**.

B4: Date of this Report

The date the report is filled out.

B5: Describe Event, Problem or Product Use Error

For an **adverse event:**

Describe the event in detail, including a description of what happened and a summary of all relevant clinical information (medical status prior to the event; signs and/or symptoms; differential diagnosis for the event in question; clinical course; treatment; outcome, etc.). If available and if relevant, include synopses of any office visit notes or the hospital discharge summary. To save time and space (and if permitted by your institution), please attach copies of these records with any confidential information deleted. **Do not identify any patient, physician, or institution by name. The reporter's identity should be provided in full in Section G.**

(continued on next page)

SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR *(continued)*

Information as to any environmental conditions that may have influenced the event should be included, particularly when (but not exclusive to) reporting about a device.

- Results of relevant tests and laboratory data should be entered in block **B6**. (See instructions for **B6**.)
- Preexisting medical conditions and other relevant history belong in block **B7**. Be as complete as possible, including time courses for preexisting diagnoses (see instructions for **B7**).

If it is determined that reuse of a medical device labeled for single use may have caused or contributed to an adverse patient outcome, please report in block **B5** the facts of the incident and the perceived contribution of reuse to the occurrence.

For a product problem: Describe the problem (quality, performance, or safety concern) in sufficient detail so that the circumstances surrounding the defect or malfunction of the medical product can be understood.

- If available, the results of any evaluation of a malfunctioning device and, if known, any relevant maintenance/service information should be included in this section.
- For a medication or special nutritional product problem, please indicate if you have retained a sample that would be available to FDA.

For a product use error: Describe the sequence of events leading up to the error in sufficient detail so that the circumstances surrounding the error can be understood.

- **For Medication Use Errors:** Include a description of the error, type of staff involved, work environment in which the error occurred, indicate causes or contributing factors to the error, location of the error, names of the products involved (including the trade (proprietary) and established (proper) name), manufacturer, dosage form, strength, concentration, and type and size of container.

- **For Medical Device Use Errors:** Report circumstances or events that could cause use errors. Medical device use errors usually occur for one or more of the following reasons:

  - Users expect devices to operate differently than they do.
  - Product use is inconsistent with user's expectations or intuition.
  - Product use requires physical, perceptual, or cognitive abilities that exceed those of the user.
  - Devices are used in ways not anticipated by the manufacturer.
  - Product labeling or packaging is confusing or inadequate.
  - The environment adversely affects or influences device use.

For a problem with a different manufacturer of the same medicine:

Please include specific information relative to the switch between different manufacturers of the same medicine, to include, but not be limited to, the names of the manufacturers, length of treatment on each manufacturer's product, product strength, and any relevant clinical data.

B6: Relevant Tests/Laboratory Data, Including Dates

Please provide all appropriate information, including relevant negative test and laboratory findings, in order to most completely convey how the medical work-up/assessment led to strong consideration of medical product-induced disease as etiology for clinical status, as other differential diagnostic considerations were being eliminated.

Please include:

- Any relevant baseline laboratory data prior to the administration or use of the medical product
- All laboratory data used in diagnosing the event
- Any available laboratory data/engineering analyses (for devices) that provide further information on the course of the event

If available, please include:

- Any pre- and post-event medication levels and dates (if applicable)
- Synopses of any relevant autopsy, pathology, engineering, or lab reports

If preferred, copies of any reports may be submitted as attachments, with all confidential information deleted. **Do not identify any patient, physician or institution by name.** The initial reporter's identity should be provided in full in **Section G.**

B7: Other Relevant History, Including Preexisting Medical Conditions

Knowledge of other risk factors can help in the evaluation of a reported adverse event. If available, provide information on:

- **Other known conditions in the patient, e.g.,**
  - Hypertension (high blood pressure)
  - Diabetes mellitus
  - Liver or kidney problems

- **Significant history**
  - Race
  - Allergies
  - Pregnancy history
  - Smoking and alcohol use, drug abuse
  - Setting

SECTION C: PRODUCT AVAILABILITY

Product available for evaluation? (Do not send the product to FDA.)
To evaluate a reported problem with a medical product, it is often critical to be able to examine the product. Please indicate whether the product is available for evaluation. Also indicate if the product was returned to the manufacturer and, if so, the date of the return.

SECTION D: SUSPECT PRODUCT(S)

For adverse event reporting:

A suspect product is one that you suspect is associated with the adverse event. In **Section F** enter other concomitant medical products (drugs, biologics including human cells, tissues, and cellular and tissue-based products (HCT/Ps), medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

Up to two (2) suspect products may be reported on one form (#1=first suspect product, #2=second suspect product). Attach an additional form if there were more than two suspect products associated with the reported adverse event.

For product quality problem reporting:

A suspect product is the product that is the subject of the report. A separate form should be submitted for each individual product problem report.

Identification of the labeler/distributor and pharmaceutical manufacturer and labeled strength of the product is important for prescription or non-prescription products.

This section may also be used to report on special nutritional products (e.g., dietary supplements, infant formula or medical foods), cosmetics, human cells, tissues, or cellular and tissue-based products (HCT/Ps) or other products regulated by FDA.

If reporting on a special nutritional or drug product quality problem, please attach labeling/packaging if available.

If reporting on a special nutritional product only, please provide directions for use as listed on the product labeling.

D1: Name, Strength, Manufacturer

Use the trade/brand name. If the trade/brand name is not known or if there is no trade/brand name, use the generic product name and the name of the manufacturer or labeler. These names are usually found on the product packaging or labeling. Strength is the amount in each tablet or capsule, the concentration of an injectable, etc. (such as "10mg", "100 units/cc", etc.).

For human cells, tissues, and cellular and tissue-based products (HCT/Ps), please provide the common name of the HCT/P. You can also indicate if the HCT/P has a proprietary or trade name. Examples: Achilles tendon, Iliac crest bone or Islet cells.

D2: Dose or Amount, Frequency, Route

Describe how the product was used by the patient (e.g., 500 mg QID orally or 10 mg every other day IV). For reports involving overdoses, the amount of product used in the overdose should be listed, not the prescribed amount. (See **APPENDIX** for list of **Routes of Administration** on the next page.)

D3: Dates of Use

Provide the date administration was started (or best estimate) and the date stopped (or best estimate). If no dates are known, an estimated duration is acceptable (e.g., 2 years) or if therapy was less than one day, then duration is appropriate (e.g., 1 dose or 1 hour for an IV).

For human cells, tissues, and cellular and tissue-based products, provide the date of transplant and if applicable, the date of explanation.

D4: Diagnosis or Reason for Use (Indication)

Provide the reason or indication for which the product was prescribed or used in this particular patient.

D5: Event Abated After Use Stopped or Dose Reduced

If available, this information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide supporting lab tests and dates, if available, in block **B6**.

D6: Lot #

If known, include the lot number(s) with all product quality problem reports, or any adverse event report with a biologic, or medication.

D7: Expiration Date

Please include if available.

(continued on next page)

SECTION D: SUSPECT PRODUCT(S) *(continued)*

D8: Event Reappeared After Reintroduction

This information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide a description of what happened when the drug was stopped and then restarted in block **B5**, and any supporting lab tests and dates in block **B6**.

D9: NDC # or Unique ID

The national drug code (NDC #) is requested only when reporting a drug product problem. Zeros and dashes should be included as they appear on the label. NDC # can be found on the original product label and/or packaging, but is usually not found on dispensed pharmacy prescriptions.

If the product has a unique or distinct identification code, please provide this here. This is applicable to human cells, tissues, and cellular and tissue-based products (HCT/Ps).

Appendix - Routes of Administration

Auricular (otic) 001
Buccal 002
Cutaneous 003
Dental 004
Endocervical 005
Endosinusial 006
Endotracheal 007
Epidural 008
Extra-amniotic 009
Hemodialysis 010
Intra corpus cavernosum 011
Intra-amniotic 012
Intra-arterial 013
Intra-articular 014
Intra-uterine 015
Intracardiac 016
Intracavernous 017
Intracerebral 018
Intracervical 019
Intracisternal 020
Intracorneal 021
Intracoronary 022
Intradermal 023
Intradiscal (intraspinal) 024
Intrahepatic 025
Intralesional 026
Intralymphatic 027
Intramedullar (bone marrow) 028
Intrameningeal 029
Intramuscular 030
Intraocular 031
Intrapericardial 032
Intraperitoneal 033
Intrapleural 034
Intrasynovial 035
Intratumor 036
Intrathecal 037
Intrathoracic 038
Intratracheal 039
Intravenous bolus 040
Intravenous drip 041
Intravenous (not otherwise specified) 042
Intravesical 043
Iontophoresis 044
Occlusive dressing technique 045
Ophthalmic 046
Oral 047
Oropharingeal 048
Other 049
Parenteral 050
Periarticular 051
Perineural 052
Rectal 053
Respiratory (inhalation) 054
Retrobulbar 055
Subconjunctival 056
Subcutaneous 057
Subdermal 058
Sublingual 059
Topical 060
Transdermal 061
Transmammary 062
Transplacental 063
Unknown 064
Urethral 065
Vaginal 066

SECTION E: SUSPECT MEDICAL DEVICE

The suspect medical device is 1) the device that may have caused or contributed to the adverse event or 2) the device that malfunctioned.

In **Section F**, report other concomitant medical products (drugs, biologics including HCT/Ps, medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

If more than one suspect medical device was involved in the event, complete all of **Section E** for the first device and attach a separate completed **Section E** for each additional device.

If the suspect medical device is a single-use device that has been reprocessed, then the reprocessor is now the device manufacturer.

E1: Brand Name

The trade or proprietary name of the suspect medical device as used in product labeling or in the catalog (e.g., Flo-Easy Catheter, Reliable Heart Pacemaker, etc.). This information may 1) be on a label attached to a durable device, 2) be on a package of a disposable device, or 3) appear in labeling materials of an implantable device. Reprocessed single-use devices may bear the Original Equipment Manufacturer (OEM) brand name. If the suspect device is a reprocessed single-use device, enter "NA".

E2: Common Device Name

The generic or common name of the suspect medical device or a generally descriptive name (e.g., urological catheter, heart pacemaker, patient restraint, etc.). Please do not use broad generic terms such as "catheter", "valve", "screw", etc.

E3: Manufacturer Name, City and State

If available, list the full name, city and state of the manufacturer of the suspected medical device. If the answer of block **E8** is "yes", then enter the name, city and state of the reprocessor.

E4: Model #, Catalog #, Serial #, Lot #, Expiration Date, Other #

If available, provide any or all identification numbers associated with the suspect medical device exactly as they appear on the device or device labeling. This includes spaces, hyphens, etc.

Model #:

The exact model number found on the device label or accompanying packaging.

Catalog #:

The exact number as it appears in the manufacturer's catalog, device labeling, or accompanying packaging.

Serial #:

This number can be found on the device label or accompanying packaging; it is assigned by the manufacturer, and should be specific to each device.

Lot #:

This number can be found on the label or packaging material.

Expiration Date (mm/dd/yyyy):

If available, this date can often be found on the device itself or printed on the accompanying packaging.

Other #:

Any other applicable identification number (e.g., component number, product number, part bar-coded product ID, etc.)

E5: Operator of Device

Indicate the type (not the name) of person operating or using the suspect medical device on the patient at the time of the event as follows:

- Health professional = physician, nurse, respiratory therapist, etc.
- Lay user/patient = person being treated, parent/spouse/friend of the patient
- Other = nurses aide, orderly, etc.

E6: If Implanted, Give Gate (mm/dd/yyyy)

For medical devices that are implanted in the patient, provide the implant date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

E7: If Explanted, Give Date (mm/dd/yyyy)

If an implanted device was removed from the patient, provide the explantation date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

E8: Is this a Single-use Device that was returned before Reprocessed and Reused on a Patient?

Indicate "Yes" or "No".

E9: If Yes to Item No. 8, Enter Name and Address of Reprocessor

Enter the name and address of the reprocessor of the single-use device. Anyone who reprocesses single-use devices for reuse in humans is the manufacturer of the reprocessed device.

SECTION F: OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)
Information on the use of concomitant medical products can frequently provide insight into previously unknown interactions between products, or provide an alternative explanation for the observed adverse event. Please list and provide product names and therapy dates for any other medical products (drugs, biologics including HCT/Ps, medical devices, etc.) that the patient was using at the time of the event. Do not include products used to treat the event.

SECTION G: REPORTER

FDA recognizes that confidentiality is an important concern in the context of adverse event reporting. The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. However, to allow for timely follow-up in serious cases, the reporter's identity may be shared with the manufacturer unless specifically requested otherwise in block G5. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

G1: Name, Address, Phone #, E-mail

Please provide the name, mailing address, phone number and E-mail address of the person who can be contacted to provide information on the event if follow-up is necessary. While optional, providing the fax number would be most helpful, if available. This person will also receive an acknowledgment letter from FDA on receipt of the report.

G2: Health Professional?

Please indicate whether you are a health professional (e.g., physician, pharmacist, nurse, etc.) or not.

G3: Occupation:

Please indicate your occupation (particularly type of health professional), and include specialty, if appropriate.

G4: Also Reported to:

Please indicate whether you have also notified or submitted a copy of this report to the manufacturer and/ or distributor of the product, or, in the case of medical device reports only, to the user facility (institution) in which the event occurred. This information helps to track duplicate reports in the FDA database.

G5: Release of reporter's Identity to the manufacturer

In the case of a serious adverse event, FDA may provide name, address and phone number of the reporter denoted in block **G1** to the manufacturer of the suspect product. If you do not want your identity released to the manufacturer, please put an X in this box.

U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Safety

What is a Serious Adverse Event?

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is:

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Links on this page:

- Accessibility
- Contact FDA

Section 12.5 SAE Reporting to IRB/REB's

Purpose
The objectives of this SOP are to describe the procedures used by the Houston Data Coordinating Center (HDCC) to facilitate accurate and timely IRB/REB reporting of serious adverse events (SAEs) occurring at PROPPR clinical sites (per individual institution's reporting policies).

Scope
This SOP applies to all PROPPR site coordinators and HDCC staff involved in SAE reporting. This SOP includes the process and activities related to the dissemination of information related to SAEs and the accurate and timely reporting of these events to the site IRB/REB's per their local institution review board policies.

References
CFR 312.32 – IND Safety Reports
CFR 312.66 – Assurance of IRB Review
ICH Guidelines for Good Clinical Practice (E6) section 3.1 – Responsibilities
ICH Guidelines for Good Clinical Practice (E6) section 4.3 – Medical Care of Trial Subjects
ICH Guidelines for Good Clinical Practice (E6) section 4.4 – Communication with IRB/IEC
ICH Guidelines for Good Clinical Practice (E6) section 4.10 – Progress Reports
ICH Guidelines for Good Clinical Practice (E6) section 4.11 – Safety Reporting
FDA Guidance: MedWatch Form 3500A, November 2005
FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs- Improving Human Subjects Protection, January 2009
FDA Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, September 2010

Definitions
SAE- Severe Adverse Event
HDCC- Houston Data Coordinating Center
IRB- Institutional Review Board
REB - Research Ethics Board (Health Canada)
ROC - Resuscitation Outcomes Consortium
SMC - Safety Monitoring Committee
DSMB – Data Safety Monitoring Board

Responsibilities
The Site Study Coordinator is responsible for:
Timely and accurate reporting of SAEs to the HDCC
Provide supporting documentation to the HDCC within a timely manner
Reporting the SAE to the local IRB/REB(s) within the required reporting time frames for Local or Non Local Serious Adverse Events, typically 10 calendar days from the time the event was discovered.
Maintaining copies in the regulatory binder of all correspondence between the site team and the IRB/REB regarding the reporting of the event. Copies of the documentation are also to be forwarded to the HDCC. This would include:

- A copy of the submission
- Any requests for further information by the board
- Acknowledgment by the board regarding any (if applicable) further required actions.

The HDCC Program Manager/Regulatory Documents Coordinator is responsible for:

- Submitting the IND Safety Report to the FDA and Health Canada
- Submitting the IND Safety Report to the HDCC's IRB
- Providing the Site Research Coordinator with copies of the IND Safety Report for submission via their institutional board
- Submitting semi-annual blinded DSMB reports through the ROC SMC and minutes to the HDCC's IRB which provide information on all new SAEs across participating PROPPR clinical sites
- Providing the Site Research Coordinator with copies of the semi-annual blinded DSMB reports and minutes and ROC SMC minutes for submission via their IRB/REB policies
- Collecting and tracking site IRB/REB submissions involving SAEs, ROC SMC, and DSMB reports and minutes.

Procedures

Local SAE Reporting (IRB/REB reporting at the site where the event occurred):

1. SAEs occurring at an individual center must be reported by the site research coordinator to the local IRB/REB(s) per the board's reporting polices and timelines.
2. Site research coordinator will forward any correspondence regarding the submission of the event to the HDCC.
3. The HDCC program manager/regulatory documents coordinator collects and tracks correspondence related to each reported event until successful review by the site's IRB/REB. SAE reports will be reviewed, as needed, by the independent medical monitor per the safety monitoring plan included in this manual.

Note:

During onsite monitoring visits, the Monitor will review site regulatory binders for appropriate documentation of SAE submission, as well as to ensure that the HDCC has received the relevant correspondence.

Sites may or may not be required by their IRB/REB to report SAEs in subjects participating at sites external to their institution.

Section 12.6 PROPPR Cause of Death Definitions

1) **Exsanguination / Hemorrhagic Shock**
Exsanguination: death caused by uncontrolled bleeding.
Hemorrhagic Shock: shock associated with the sudden and rapid loss of significant amounts of blood. Severe traumatic injuries often cause such blood losses. This results in inadequate perfusion to meet the metabolic demands of cellular function. Hemorrhagic death occurs within a relatively short time (usually during active resuscitation) after admission unless transfusion quickly restores normal blood volume. Occasionally rebleeding may occur, resulting in later deaths.

2) **Traumatic Brain Injury (TBI)**
An injury to the brain caused by penetration of the skull or movement of the brain within the skull. TBI as a cause of death usually occurs with several days of admission. TBI death is directly related to: (1) a TBI deemed non-survivable and documented as such by a faculty physician; (2) rapid deterioration and cardiovascular collapse following hemodynamic changes consistent with herniation, or (3) brain death.

3) **Respiratory/Pulmonary Contusion/Tension Pneumothorax**
Respiratory: any loss of ventilatory capability, usually from a mechanical issue somewhere between the ventilator and the pulmonary parenchyma.
Pulmonary contusion: injury to lung parenchyma, leading to edema and blood collecting in alveolar spaces and loss of normal lung structure & function. This lung injury develops over the course of 24 hours, leading to poor gas exchange, increased pulmonary vascular resistance and decreased lung compliance. Usually death will occur within hours of injury. (MedicineNet.com)
Tension Pneumothorax: The accumulation of air under pressure in the pleural space causing death within minutes. (MedicineNet.com)

4) **Sepsis** – An overwhelming systemic response to documented infection. Patients dying of sepsis usually do so > 72 hours after admission.

5) **MOF** – Altered organ function in at least 2 organ systems. Progressive and profound organ dysfunction that is incompatible with life. Patients dying of MOF usually do so > 48 hours after admission.

6) Stroke
New neurological deficit not present prior to injury which is sudden or rapid in onset, lasts > 24 hours and is confirmed as an infarction by CT or MRI, acutely causing death. (TRDB, 2007)

7) **Myocardial Infarction**
Acute, irreversible myocardial injury documented by both: (1) Abnormal increase in CK-MB or troponin and (2) New, serial T-wave, S-T segment or Q wave ECG abnormalities acutely causing death. (TRDB, 2007)

8) **Pulmonary Embolism** - A blood clot lodged in the lumen of a pulmonary artery acutely causing death, diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan. (TRDB, 2007)

9) **Transfusion Related Fat**ality – fatality as a direct result of a complication of blood component transfusion. Refer to the 13 transfusion related complications. (Practice Guidelines for Blood Transfusion)

Section 12.7 Death Adjudication

Section 12.7.1 Documents Required for Death Adjudication

It is expected that patients enrolled in PROPPR will have a significant mortality rate. It is likely that subjects will have multiple causes of death, especially those that occur after 72 hours. We require that site PI's and study coordinators discuss each death and use the following categories to assign causality.

In the event of a subject death, the local site PI will determine the cause of death using the following categories; Exsanguination/Hemorrhagic Shock, Traumatic Brain Injury (TBI), Respiratory/Pulmonary Contusion/Tension Pneumothorax, Sepsis, Multi Organ Failure (MOF), Cardiovascular Event, Pulmonary Embolism, Transfusion Related Fatality, or other, unknown. Note Section 16.2 of the MOO for definitions.

Redacted records will be sent to the DCC to facilitate accurate death reconciliation. These records include: 1st 24 hour operative notes, anesthesia records and CT scan reports, admission history and physical, discharge summary, death summary and autopsy reports and any other important supporting documents from the site PI. Site PI's will submit a short paragraph within 2 weeks of the death summarizing the data supporting the final cause(s) of death. Timing of withdrawal of care (if applicable); will be noted in the assessment.

The HDCC will review the death adjudication packet and attach the subject's CRF form #17 along with the death adjudication CRF form #25. The documents will then be forwarded to the HCCC PI and/or Medical Monitor for review.

The HCCC PI will review the cause of death assessment and all available de-identified clinical documents such as the initial H&P, operative notes, discharge summary, death note, etc. The HCCC PI will remain blinded to the PROPPR group assignment. The HCCC PI will complete CRF form #25 indicating the cause of death using the categories mentioned above and will forward the report to the HDCC.

The HDCC will compare the Site PI and HCCC PI cause of death assignments, and if in agreement, will be accepted as the cause of death for that individual subject. If there is disagreement for cause of death, the same redacted and de-identified information will be forwarded to the Medical Monitor for review. The Medical Monitor may discuss the case with either the Site or HCCC PI, but must remain blinded to the PROPPR treatment group assignment. The Medical Monitor's assessment will be considered the final cause of death for that individual subject.

The adjudication process described above will be used for all clinical sites with the exception of the Houston clinical site. The Medical Monitor will review the site PIs cause of death assignment. The Medical Monitors assessment will be considered final. The HCCC PI will not participate in death adjudication for Houston subjects.

Cause of deaths requiring adjudication from the Medical Monitor will be summarized and reported in aggregate to the DSMB. The death adjudication CRF form #25 will be used for cause of death analysis.

Section 12.8 Independent Medical Monitor's Role

An independent medical monitor will review all unexpected problems involving risk to subjects or others, SAEs and all transfusion-related deaths and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a SAE or transfusion-related death, comment on the relationship to participation in the trial. If the death is considered unexpected and is either suspected or probably due to treatment, this event would be promptly reported to the medical monitor and the DSMB. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for serious adverse events determined by either the investigator or medical monitor to be possibly or definitely related to participation must be promptly reported per FDA and/or Health Canada guidelines.

Section 12.9 Data Safety Monitoring Board (DSMB)

Section 12.9.1 DSMB Role

The DSMB for PROPPR is an NHLBI appointed group of experts assigned to review all ROC protocols. The principal role of the DSMB is to regularly monitor the data from the clinical trial, review and assess the performance of its operations, and make recommendations, as appropriate, to the Institute with respect to:

- the performance of individual centers (including possible recommendations on actions to be taken regarding any center that performs unsatisfactorily);
- interim results of the study for evidence of efficacy or adverse effects;
- possible early termination of the trial because of early attainment of study objectives, safety concerns, or inadequate performance;
- desirability of proceeding to the full-scale trial at the completion of the vanguard phase; and
- possible modifications in the clinical trial protocol.

Thus, the DSMB must provide a multidisciplinary and objective perspective, expert attention to the many factors during the course of the trial, and considerable judgment.

Section 12.9.2 DSMB Process for Interim Analysis and Ongoing Safety Review

There will be three formal analyses. The 2 interim analyses for the DSMB will occur after 1/3 and 2/3 of the projected 24-hour or 30-day mortality events are observed (whichever reaches its projected 1/3 and 2/3 first). The two co-primary outcomes will be separately monitored using a two-sided O'Brien-Fleming boundary with Lan-DeMets alpha spending function based on events for each of the two comparisons. The plan for interim analysis is suggested as a guideline for the DSMB, and could be modified by the DSMB prior to the start of the trial.

At each DSMB meeting after the start of the trial, we will present safety data by treatment group (labeled as A, B in the same manner proposed by the 2006 FDA Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees, unless the DSMB requires complete unblinding). This would include, but is not limited to, total counts of all related, serious and unanticipated adverse events, including a description of the event itself. Additional safety analyses will be developed as requested by the DSMB. We will report overall mortality for the safety analysis. At the formal interim analysis we will report mortality by treatment group (or A,B).

Open (blinided) DSMB reports will be submitted to clinical sites for IRB submission.

Section 12.10 Clinical Site Monitoring

Purpose
To describe the procedure by which clinical investigations are monitored to ensure that clinical investigations are conducted in compliance with the protocol, Sponsor policies, the applicable FDA and Health Canada regulations, and principles of Good Clinical Practice. To provide a tool for training monitors in the procedure by which clinical investigations are monitored by the PROPPR HDCC.

Scope
This SOP applies to all clinical site personnel involved with data collection and/or data entry, the study monitor(s) responsible for source document verification, and the HDCC.

References
FDA Inspections, Part III.
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm
FDA Guidance for Industry: Electronic Source Documentation in Clinical Investigations, December 2010
OHRP Guidance on Reviewing and Reporting Unanticipated Problems
http://www.hhs.gov/ohrp/policy/advevntguid.html

21 CRF 812.43(c)
ICH Guidelines for Good Clinical Practice (E6) Section 4.2 – Adequate Resources
ICH Guidelines for Good Clinical Practice (E6) Section 4.3 – Medical Care of Trial Subjects
ICH Guidelines for Good Clinical Practice (E6) Section 4.4 – Communication with IRB/IEC
ICH Guidelines for Good Clinical Practice (E6) Section 4.5 – Compliance with Protocol
ICH Guidelines for Good Clinical Practice (E6) Section 4.6 – Investigational Products
ICH Guidelines for Good Clinical Practice (E6) Section 4.9-Records and Reports
ICH Guidelines for Good Clinical Practice (E6) Section 5.12 – Information on Investigational Products
ICH Guidelines for Good Clinical Practice (E6) Section 5.18 – Monitoring

Definitions
AE – Adverse Event
CAP – Corrective Action Plan
HDCC – Houston Data Coordinating Center
HCCC PI – Houston Clinical Coordinating Center Principle Investigator
HDCC PI – Data Coordinating Center Principal Investigator
PI – Principal Investigator
ROC – Resuscitation Outcomes Consortium
SAE – Serious Adverse Event
IRB - Institutional Review Board
REB - Research Ethics Board (Health Canada)

Responsibilities
It is the responsibility of clinical site personnel to follow the IRB/REB approved protocol and conduct the study in accordance with institutional policies & procedures, State and Federal regulations, and GCP guidelines.

It is the responsibility of the study monitor to ensure that the investigator understands the applicable regulatory requirements and Good Clinical Practices; to supply training when appropriate; and to draft corrective action/preventative action (CAP) plans when needed.

It is the responsibility of the HDCC PI and program manager to:

- Ensure that the investigative site complies with the applicable regulatory requirements and Good Clinical Practices and to implement CAP plans as needed.
- Inform the appropriate study officials (e.g., IND Sponsor, funding Sponsor, Study Chair, etc.) of significant compliance issues of investigative sites.

Procedures

Data Validation

During monitoring site visits, an examination of the study data will be performed. Source documents will be compared with information in the eCRF database and discrepancies flagged for clarification. The monitored review will verify that data was collected according to the IRB/REB approved protocol. The data will also be examined for trends, especially with respect to AE/SAE's. Any discrepancies, questions, missing data or errors that arise are resolved or will be changed via the e-CRF process described in chapter 16.

Data Change Clarification Requests

When questions concerning subject information arise during monitoring of the PROPPR study, the e-CRF questions will be flagged by the study monitor in the e-CRF. All queries will be resolved, if possible, during the visit. The e-CRF database will maintain a detailed audit trail of all changes. Information on database correction and change procedures can be found in Chapter 16 of the MOO.

Protocol Compliance

Verification of Protocol Compliance:

- The study monitor will review medical records to confirm that each subject enrolled meets eligibility criteria.
- That eligible subjects are not being excluded will be verified by reviewing the log of excluded subjects with the study coordinator, if applicable.
- Verify that randomization procedures are correct and the blind is being maintained.
- Confirm that timing of study procedures are being carried out as specified.
- Verify that adverse events, serious adverse events, and unanticipated problems are being appropriately reported and documented.
- Delegation of responsibility log is complete, current, and accurate
- Protocol violations will be documented in detail in the site visit report and follow-up letter to the PI.

Deviations from the Protocol (See Section 12.13)

- Any deviations from the protocol must be documented, showing the dates of, and any reasons for, each deviation from the protocol, as well as any CAPs taken.
- PI will be informed of all deficiencies during the interim visit (if at all possible) and in the follow-up letter to the site. Protocol deviations may also need to be reported to the IRB.

Noncompliance

- If the Study Monitor discovers that a PI is non-compliant, the Study Monitor will attempt to promptly secure compliance.
- The Study Monitor will notify the Sponsor immediately.
- After consultation with the Sponsor, the Study Monitor may be required to draft and implement a CAP plan, which may include training of the investigative site personnel.
- If compliance cannot be secured by the Study Monitor, the HDCC PI, in collaboration with the HCCC and ROC PI, will work directly with the site PI and research coordinator to implement a CAP plan.

Regulatory Documents

The required regulatory documents, which should be maintained in the Site Regulatory binders/files, must be both current and complete (cover the entire duration of the study at the site being monitored, note Chapter 13 for the MOO for a detailed list). The Study Monitor will check that all required regulatory documents are present, and retrieve copies of any outstanding documents for the HDCC files.

Site Number: ___ ___	Visit Date: / /	Monitor Signature:

Description of Problem	CODE	Date of Event	Date IRB Notified *(if applicable)*	Reported to HDCC Prior to Monitored Visit?	Principle Investigator's Signature
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature: Date:
		/ /	/ /	□ Yes □ No	Signature:

Section 12.10.1 Monitoring of Informed Consent

Purpose
The purpose of this standard operating procedure (SOP) is to outline the Informed Consent verification process and to provide a tool for clinical sites and study monitors.

Scope
The procedures outlined apply to all clinical study personnel and study monitor(s) SOP applies to the CRA who will be responsible for ensuring the adequacy of the process by which the Site PI obtains Informed Consent.

References
FDA Inspections, Part III.
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133569.htm

OHRP Guidance on Reviewing and Reporting Unanticipated Problems
http://www.hhs.gov/ohrp/policy/advevntguid.html

Code of Federal Regulations 21CFR § 50.20 – General Requirements for Informed Consent
Code of Federal Regulations 21CFR § 50.23 – Exception from General Requirements
Code of Federal Regulations 21CFR § 50.27 – Documentation of Informed Consent
Code of Federal Regulations 45CFR § 46.116 – General Requirements for Informed Consent
Code of Federal Regulations 45CFR § 46.117 – Documentation of Informed Consent
FDA Guidance for IRB's, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research, March 2011
FDA Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues, September 21, 2010
FDA Guidance on Research Involving Coded Private Information or Biological Specimens, October 16, 2008
FDA Guidance on Exculpatory Language in Informed Consent, August 19, 2011
ICH Guidelines for Good Clinical Practice (E6) Section 1.28 – Informed Consent
ICH Guidelines for Good Clinical Practice (E6) Section 1.37 – Legally Authorized Representative
ICH Guidelines for Good Clinical Practice (E6) Section 4.8 – Informed Consent of Trial Subjects

Definitions
PI – Principal Investigator
IRB – Institutional Review Board
REB - Research Ethics Board (Health Canada)
ICF – Informed Consent Form
HDCC – Houston Data Coordinating Center
LAR – Legally Authorized Representative

Responsibilities
It is the responsibility of clinical site personnel to follow the IRB/REB approved protocol and conduct the study in accordance with institutional policies & procedures, State and Federal regulations, and GCP guidelines.

It is the responsibility of the study monitor to review and verify that no subjects were enrolled before IRB/REB Approval. The site PI may determine whether potential subjects would be interested in participating in an investigation, but shall not request written Informed Consent from any subject to participate in the research study before obtaining IRB/REB approval.

The study monitor is also responsible for reporting to the HDCC if subjects were treated without obtaining proper Informed Consent.

Procedure
Documenting Informed Consent: The study monitor will verify the following items during monitoring visits:

- A signed and dated ICF was obtained from every subject and/or LAR enrolled in the study.
- Only the current version of the IRB approved ICF form was used.
- Documentation of all attempts to obtain informed consent from the subject and/or LAR.
- Documentation of the informed consent process including but not limited to discussion of study procedures, risks and benefits, opportunity for the subject and or LAR to ask questions, and documentation the subject or LAR received a copy of the ICF.
- Site procedures for consenting non-English speaking subjects and or LAR.
- Site specific consent procedures (if applicable) for use of the research blood samples in screening failures.

Section 12.11 Site Close-Out Visit

Purpose
To define procedures for the clinical site close-out visit and the required documentation associated with these activities. The purpose of the close-out visit is to:

- Verify the proper disposition of study equipment (if applicable)
- Verify / collect final site IRB/REB documents related to study closure
- Verify all data queries have been resolved
- Ensure that study records and data are accurate and complete
- Retrieve final copies of completed site regulatory documents / logs
- Ensure that regulatory requirements for records retention are understood by the study staff.

Scope
The procedures apply to all PROPPR clinical site research personnel and the HDCC personnel and/or designee (primarily contract CRO monitors) involved in the conduct of close-out monitoring visits.

References
21 CFR 312.44 – Termination
21 CFR 312.57 – Recordkeeping and Retention
21 CFR 312.58 – Inspection of Sponsor Records and Reports
21 CFR 312.59 – Disposition of Unused Supply of Investigational Drug
ICH Guidelines for Good Clinical Practice (E6) Section 4.3 – Medical Care of Trial Subjects
ICH Guidelines for Good Clinical Practice (E6) Section 4.4 – Communication with IRB/IEC
ICH Guidelines for Good Clinical Practice (E6) Section 4.5 – Compliance with Protocol
ICH Guidelines for Good Clinical Practice (E6) Section 5.12 – Information on Investigational Products
ICH Guidelines for Good Clinical Practice (E6) Section 5.5 – Trial Management, Data Handling, Record Keeping, and Independent Data Monitoring Committee
ICH Guidelines for Good Clinical Practice (E6) Section 5.18 – Monitoring
ICH Guidelines for Good Clinical Practice (E6) Section 5.22 – Clinical Trial/ Study Reports

Definitions
CRO - Contract Research Organization
IRB - Institutional Review Board
REB - Research Ethics Board (Health Canada)
HDCC – Data Coordinating Center
HDCC PI – Data Coordinating Center Principal Investigator
PI - Principle Investigator

Responsibilities
The HDCC study monitor or designee (CRO Monitor) will conduct, document and process all monitoring activities for specific studies they are assigned according to the study specific Monitoring Plan, including the close-out visit.

The HDCC program manager and regulatory documents coordinator are responsible for ensuring that all data and regulatory document clarification/change requests have been resolved prior to the close-out visit.

The HDCC and/or designee are responsible for scheduling the visit with clinical site personnel and ensuring

that all materials necessary for close-out visit are available.

Site PIs are responsible for ensuring that their key staff is present at the close-out visit once they agree to a close-out visit date and time.

Procedure

1.1. The HDCC will identify clinical sites ready for a close-out monitoring visit and will coordinate with the study monitor to schedule the site visit.

1.2. The monitor will schedule and confirm the close-out visit with the PI and appropriate site personnel for a mutually acceptable date and time. Confirmation will (may) be sent by fax, email or mail. A copy of the confirmation correspondence will be kept in the HDCC's files for the clinical site.

1.3. The HDCC and or monitor will ensure that all materials necessary for the close-out visit have been received by the site prior to the visit, including but not limited to FDA/Health Canada notification of end of study and final DSMB reports, if applicable.

1.4. The monitor will obtain a copy of all outstanding documents identified by the HDCC.

1.5. During the close out visit, the monitor will review the Regulatory Documentation (refer to the checklist at the end of this section) for the study to ensure required documents are in the files and are current and ready to be archived. The documents to be archived should cover the time span of the study and thus, updated documents may need to be collected. If so, the monitor will do so at this visit. These documents will all versions of the following:

- Signed / dated CV and copy of current medical license for each physician investigator
- Signed / dated investigator agreement, form FDA 1572
- Signed / dated ROC financial disclosure forms
- Signed / dated protocol signature page(s) / amendment signature page(s)
- Copy of current approved protocol and any amendments
- Investigator Brochure,
- Manual of Operations
- Site IRB/REB approval, continuing review, and modification documents
- Site IRB/REB approved informed consent documents
- Correspondence to and from the reviewing IRB/REB
- IRB roster, if available, and FWA number
- Fully executed clinical trial agreement (contract)
- Study specific forms <u>as applicable</u> the specific study:
  - Site personnel and delegation log
  - Equipment accountability log(s) and shipping records.
  - Laboratory license & certification (CAP), CLIA, clinical site lab normal ranges
  - Evidence of training
  - Screening & Enrollment Log
  - Blood Bank Master Subject Log
  - Master Subject Log
  - Correspondence with Sponsor
  - Monitoring Visit Log

1.6. The monitor will review study files to ensure the following are complete, accounted for and ready for archival:

- Final screening / enrollment log(s)
- Regulatory binders and all associated documents are present

- Original ICFs for each screened / enrolled subject are present in their study files, a copy is in the medical files (enrolled subjects only) and documentation exists that a copy was given to each subject
- All adverse events (AEs) / unanticipated and serious adverse events (SAEs) have been reported to the sponsor and reviewing IRB (if required)
- Protocol violations / deviations have been reported to the sponsor and reviewing IRB (if required)
- Unanticipated problems have been reported to the sponsor and reviewing IRB (if required)
- The investigational protocol has been followed
- Any discrepancies are noted in the report

1.7. PROPPR Equipment Accountability:
- The monitor will ensure that all study related equipment is returned, destroyed, or released to the clinical site.

1.8. The monitor will meet with the PI and appropriate study staff at the close-out visit to:
- Review all completed and incomplete action items from previous visit.
- Discuss GCP and protocol compliance.
- Review all findings and problems from current monitoring visit. (If a problem cannot be resolved at the monitoring visit, the monitor will document the problem in his/her monitoring report and submit to the HDCC for appropriate follow-up).
- Discuss the investigator's role and responsibility regarding the final study report, any publications or presentations.
- Instruct the PI / staff to call the HDCC immediately if they are contacted by the FDA for an audit.

1.9. Remind the PI/staff of their obligations regarding study record storage/archival according to the applicable CFR and site agreement (contract).

1.10. The monitor will utilize a study specific report form / checklist (refer to checklist below) for documentation of the close out monitoring visit.

1.11. This report form/checklist will be completed within 10 working days of the visit and sent to HDCC PI and program manager for review/comments. The final report will be prepared based on any comments or questions and will be signed by both the monitor and HDCC PI within 20 working days of the visit. The signed copy of the final report will be filed in the site specific study files.

1.12. A follow-up letter to the PI will be prepared to document what was accomplished at the visit and list any close out action items still required. This letter will be completed and sent to the PI within 30 days of the close-out visit.

1.13. A copy of the follow-up letter will be filed in the site specific study files.

List of Essential Documents Maintained at Clinical Site

No.	Document	HDCC File	Investigator File
1	Updates of Investigator Brochure	√	√
2	Revision to Protocol + Amendments	√	√
3	Revision to Informed Consent Forms (+ translations) + Other Written Information	√	√
4	Revision to Advertisements and Community Notification Documents	√	√
5	IRB/REB Approvals	√	√
6	Regulatory Authority Approvals/Notifications, where required	√	√
7	CVs with updates as indicated	√ (copy)	√
8	Site clinical lab – normal ranges with updates as indicated	√	√
9	Clinical Lab – Certification, Accreditation	√ (copy)	√
10	Research Lab Specimen Shipping Documents	√	√
11	Monitoring Visit Reports	√	√
12	Relevant communications other than site visits	√	√
13	Signed Informed Consent Forms		√
14	Source Documents		√
15	Completed CRFs	√ (e-CRF)	√ (original)
16	SAE Reports	√	√
17	MedWatch Safety Reports	√	√
18	Safety Information Between the HDCC & Investigator	√	√
19	Interim/Annual Reports to IRB/EC and Regulatory Authorities	√	√
20	Subject Screening Log		√
21	Subject Master Enrollment Log		√
22	Subject Enrollment List		√
23	Study Site Personnel & Responsibility Log	√ (copy)	√ (original)

Section 12.12 Monitored Visit Log

PROPPR Monitor Visit Log

Date(s) of Visit mm/dd/yy	Description of Monitoring Activity (i.e. pre-site, initiation, routine, close-out)	Monitor Name & Signature	PI/Study Staff Name & Signature

Section 12.13 Site Reporting of Protocol Deviations and Unanticipated Events

Purpose
To describe procedures for reporting protocol deviations and unanticipated events to the PROPPR HDCC.

Scope
This SOP applies to all clinical site personnel, PROPPR study monitor(s), and the HCCC/HDCC.

References
OHRP Guidance on Reviewing and Reporting Unanticipated Problems
http://www.hhs.gov/ohrp/policy/advevntguid.html

21 CRF 312.43(c)
ICH Guidelines for Good Clinical Practice (E6) Section 4.2 – Adequate Resources
ICH Guidelines for Good Clinical Practice (E6) Section 4.3 – Medical Care of Trial Subjects
ICH Guidelines for Good Clinical Practice (E6) Section 4.4 – Communication with IRB/IEC
ICH Guidelines for Good Clinical Practice (E6) Section 4.5 – Compliance with Protocol
ICH Guidelines for Good Clinical Practice (E6) Section 4.9-Records and Reports
ICH Guidelines for Good Clinical Practice (E6) Section 5.18 – Monitoring

Definitions
CAP – Corrective Action Plan
HDCC – Houston Data Coordinating Center
HDCC Program Manager – Project Manager
HDCC PI – Data Coordinating Center Principal Investigator
PI – Principal Investigator
ROC – Resuscitation Outcomes Consortium
IRB - Institutional Review Board
REB - Research Ethics Board (Health Canada)

Minor Deviation – An occurrence that does not adversely affect subject safety, will not compromise the validity of the study results, and does not violate local, State, or Federal laws.

Major Deviation – An occurrence that jeopardizes subject safety, may compromise the validity of study results, or violates local, State, or Federal laws.

Unanticipated Events – Occurrences beyond the control of research personnel and not meeting the criteria for minor and major deviations defined above. Examples include a site shut down due to hurricane/blizzard/earthquake preventing screening/enrollment/ or follow-up of randomized subjects, backorder of reagent preventing a site from analyzing TEG/Multiplate samples.

Responsibilities
Clinical site personnel are responsible for following the IRB/REB approved protocol and conduct the study in accordance with institutional policies & procedures, State and Federal regulations, and GCP guidelines.

Clinical sites will follow local IRB/REB reporting procedures for protocol deviations and unanticipated events. Documents related to local IRB/REB notification and/or IRB/REB response (if applicable), will be forwarded to the PROPPR HDCC Regulatory Coordinator.

Procedures
The clinical site will submit an occurrence report (Section 12.13.1) within 5 days of discover of a protocol deviation or unanticipated event.

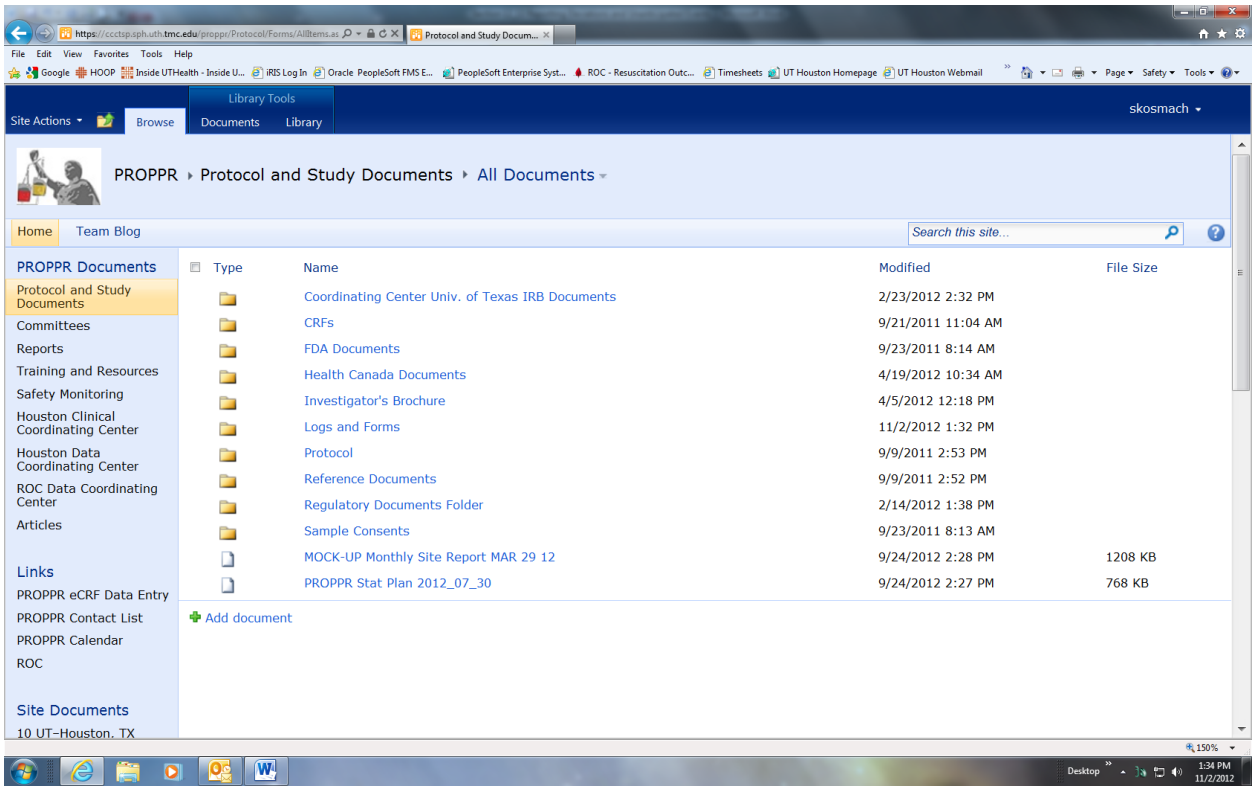
Examples of Occurrences to Report: *(Not Inclusive List)*
Protocol
Randomized Blood Products not given in order of treatment assignment.
Informed Consent
Incorrect Informed Consent: Unapproved Version
Incorrect Informed Consent: Wrong Approved Version
Incorrect Informed Consent: Wrong Study
Informed Consent Not Properly Signed or Dated by Subject/LAR
Informed Consent Not Properly Signed or Dated by Person Obtaining Consent
Informed Consent Obtained by an Unauthorized Individual list on Site 1572
Informed Consent Given by Someone Other Than the Subject's Legally Authorized Representative
Informed Consent Without Required Witness *(if required by local IRB)*
Unable to Locate Informed Consent Document (*obtained but lost*)
Enrollment
Ineligible Subject Enrolled
Screening for Eligibility Procedures Not Followed
Subject Randomized Late
Subject Randomized Prior to Screening Eligibility Procedures Completed
Randomization Procedures Not Followed
Data Collection
Data Incorrect – Not Supported by Source Documents
Data Missed – Noted in Source Documents but Not Reported
No Source Documents Found to Support Recorded Data
Window for Data Collection Missed *(too early/too late)*
Data obtained by Unauthorized Individual
Data Correction Procedures Not Followed
Data Submitted to HDCC Late
Data Queries Submitted to HDCC Late
AE/SAE's
SAE's Reported Late
SAE Reporting Procedures Not Followed
SAE Reported with Incorrect Data
SAE Reported with Missing Data
Local IRB Reporting Requirements Not Followed
SITE REGULATORY ISSUES
Failure to Maintain IRB Approval
Failure to Maintain Regulatory Documents Binder (1572, CV, License, Human Subjects Training)
Noncompliance with Monitored Visit Procedures (Visits Cancelled at Last Minute, Coordinator Not Available, Medical Record or Other Source Documents Not Available)
Study Records Unsecured/Missing
Research Lab Equipment Unsecured/Missing

Section 12.13.1 Occurrence Report

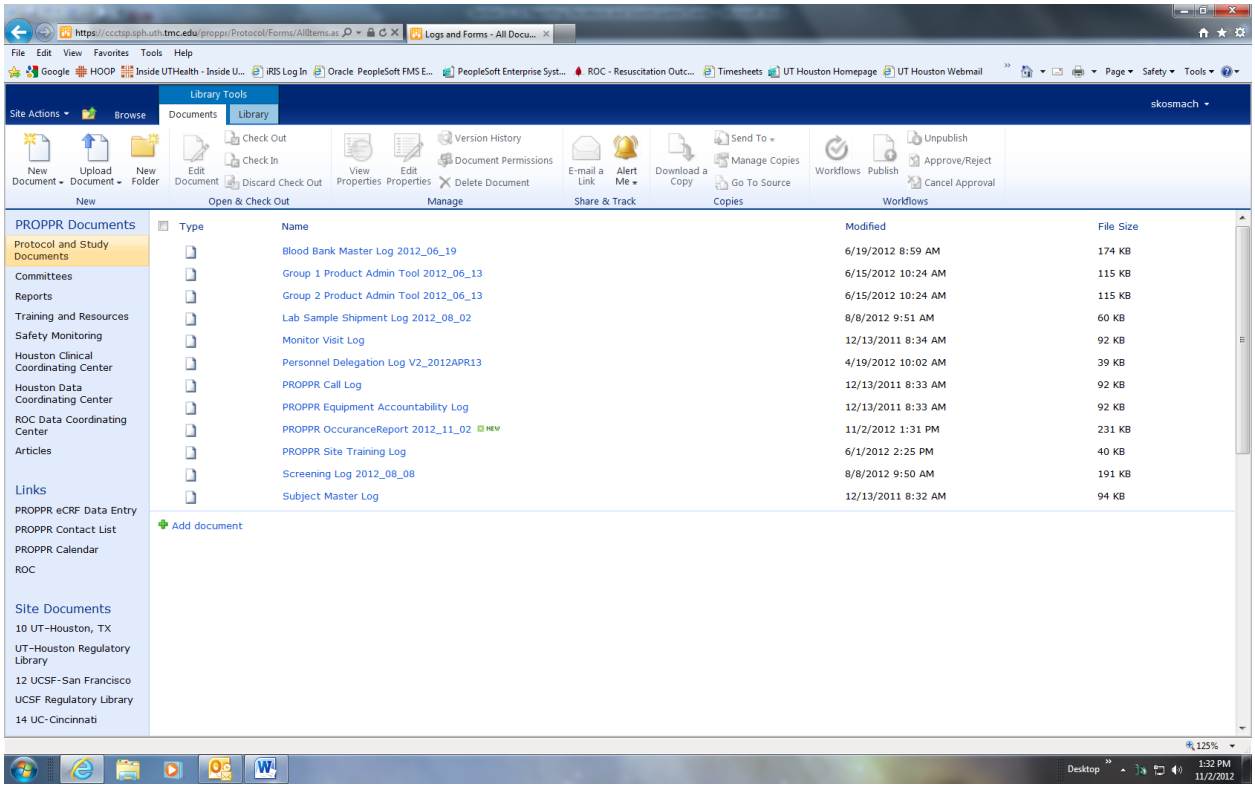
Instructions for Completion of Occurrence Report

Download the PDF document labeled “Occurrence Report” from the PROPPR SharePoint Website.

Open the Protocol and Study documents folder on the left side of the screen.



Select the subfolder “Logs and Forms”.



Select “PROPPR Occurrence Report” from the list and save the PDF to your desktop.

Open the PDF from your desktop.

Enter your site number from the drop-down list located in the upper right corner.

Enter the date of the occurrence using the drop-down calendar.

Enter the date of discover using the drop-down calendar.

Select the type of report from the drop-down list (*initial or follow-up*).

Question #1: Provide a description of the occurrence. Report multiple occurrences on separate forms.

Question #2: Indicate if the occurrence was subject-specific. If “yes”, record the study ID number in the space provided.

Question #3: Complete question #3 if the occurrence was due to a clinical care requirement or select NA.

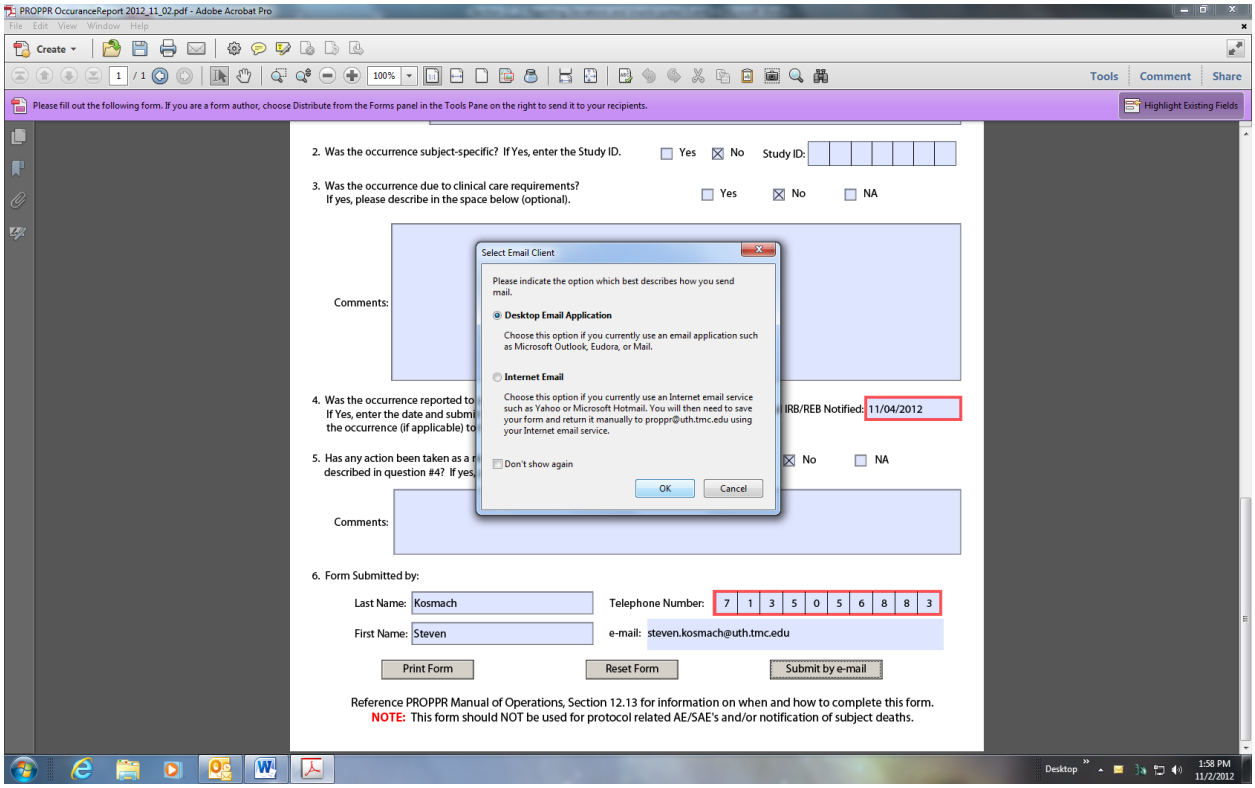
Question #4: Indicate if the occurrence was reported to your local site IRB/REB. If yes, record the date using the drop-down calendar.

Question #5: Indicate if any action has been taken as a result of the occurrence.

Question #6: Enter your contact information in the space provided. You must provide your full name, telephone number and e-mail address to submit the form electronically.

Steps to Submit the Occurrence Form

Print a copy of the form for your site regulatory folder.
Select the "submit by e-mail" button on the bottom right.
You should see the following pop-up screen:



By default, desktop E-mail application is selected. Click "OK".
The form will be delivered to the PROPPR@uth.tmc.edu mailbox.

Click the "reset" button to clear the form. *(Remember to print a copy before resetting the form!)*

If you're unable to submit the form by e-mail, a copy can be faxed to the HDCC at 713-500-9530.

The form can also be FedEx'd to the HDCC using the address below:

UTHealth, School of Public Health
Steve Kosmach
1200 Herman Pressler
RAS E819
Houston, Texas 77030

All site occurrence reports will be reviewed and categorized by the PROPPR HCCC/HDCC Coordinating Centers and reported on monthly site reports.

Clinical site monitors will review the occurrence reports and any CAP follow-up, if indicated.

The occurrence report form should not be used for reporting protocol related AE/SAE's and/or subject deaths.

PROPPR
Prospective Randomized Optimum Platelet and Plasma Ratios

Occurrence Report

For Deviations & Unanticipated Events

Site Number:

Date of Occurrence: Date Discovered: Type of Report:

1. Provide a description of the occurrence.

2. Was the occurrence subject-specific? If Yes, enter the Study ID. ☐ Yes ☐ No Study ID:

3. Was the occurrence due to clinical care requirements? If yes, please describe in the space below. ☐ Yes ☐ No ☐ NA

Comments:

4. Was the occurrence reported to your IRB/REB? If Yes, enter the date and submit the IRB/REB assessment of the occurrence (if applicable) to the HDCC. ☐ Yes ☐ No Date Local IRB/REB Notified:

5. Has any action been taken as a result of the occurrence, other than described in question #4? If yes, please describe in the space below. ☐ Yes ☐ No ☐ NA

Comments:

6. Form Submitted by:

Last Name: Telephone Number:

First Name: e-mail:

Print Form Reset Form Submit by e-mail

Reference PROPPR Manual of Operations, Section 12.13 for information on when and how to complete this form.
NOTE: This form should NOT be used for protocol related AE/SAE's and/or notification of subject deaths.

Chapter 13 - Regulatory (FDA/Health Canada & IRB/REB)

Section 13.1 Overview

Chapter 13 describes procedures related Institutional Review Boards and the FDA.

Section 13.2 IND Application & Clinicals.gov Registration

The PROPPR clinical trial was assigned the FDA IND number 14927.

Information on the PROPPR clinical trial is available at the weblink below:

Pragmatic, Randomized Optimal Platelets and Plasma Ratios - Full Text View - ClinicalTrials.gov (http://clinicaltrials.gov/ct2/show/NCT01545232?term=PROPPR&rank=1)

Section 13.3 IRB/REB Submission Process

Each investigative site will submit what is required by their local Institutional Review Board/Research Ethics Board (Canada). *University of Texas IRB* stamped approved version documents (e.g. Protocol, Investigator's Brochure, Safety Analysis Plan, Case Report Forms) and other site specific documents will be submitted by the site to their IRB/REB to track and evaluate the ethical and procedural conduct of the trial in compliance with the following:

Title 21 CFR 50: Protection of Human Subjects - Informed Consent
Title 21 CFR 56: Institutional Review Boards
Title 21 CFR 312: INDs/sponsor and investigator responsibilities
Title 45 CFR 46.101(i): Emergency Research (HHS)
ICH Guidelines for Good Clinical Practice (E6) section 4.4: Communication with IRB/IEC
61 Federal Register 51531: "Waiver of Informed Consent Requirements in Certain Emergency Research" - October 2, 1996
FDA Guidance Document: Exception from Informed Consent Requirements for Emergency Research - March 2011

Section 13.4 Documents to be Maintained at Site

Regulatory documents and other study-related documents are to be maintained at the investigational site to demonstrate the compliance of the Investigator with the standards of Good Clinical Practice and with all applicable regulatory requirements according to the following regulations and guidance:

Title 21 CFR 312.57 – Record Keeping and Record Retention
Title 21 CFR 312.62 – Investigator Record Keeping and Record Retention
Title 21 CFR 312.64 – Investigator Reports
Title 21 CFR 312.66 – Assurance of IRB Review
ICH Guidelines for Good Clinical Practice (E6) section 4.9 – Records and Reports
ICH Guidelines for Good Clinical Practice (E6) section 8 – Essential Documents for the Conduct of a Clinical Trial
Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs – Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

Each site must maintain 1 trial master file for the study, and all essential documents (regulatory, forms, correspondence) must be contained in the file based on the following:

- Documents must be generated and on file before the trial formally starts
- The regulatory binder documentation will be kept in three-ring binders
- Documents must be updated throughout the life of study and in a timely manner
- Regulatory binder(s) must be maintained in a secured area with restricted access
- Regulatory binder(s) will be made available for review during monitoring and audit visits.

Comprehensive List of Regulatory Binder Contents

Documents/Information in these sections may be found in separate binders, notebooks and/or locations and need to be cross-referenced in these sections.

The regulatory binder(s) at each investigative site will include the following essential documents:

Sec.	Essential Documents
1	**STUDY TEAM**
	Study Team Contact List
	Study Team Signature and Delegation Log
	CVs, Licenses, Financial Disclosures, Applicable Certifications of Key Study Personnel
2	**PROTOCOL**
	Study protocol + amendments
	IRB Stamped Consent Document and Translations
	IRB Stamped Advertisements
	Investigator Brochure (IB)
	Safety update letters for inclusion in IB
	IRB Stamped Community Consultation Materials
	IRB Stamped CRF's and amendments

3	**REGULATORY**
	Committee for Protection of Human Subjects (IRB) Documentation
	Local IRB Submission Forms (initial, amendments, renewals etc)
	Local IRB Outcome Letters (Approvals, Acknowledgments etc.)
	Local IRB Correspondence
	Federal Approvals (Food and Drug Administration/Health Canada)
	Form FDA 1572 for all Key Study Personnel
	Copy of IND/Health Canada Approval Letter (as applicable)
	FDA/Health Canada Correspondence
	Annual Reports

4	**PATIENT LOGS**
	Screening log
	Enrollment log
	Subject Visit Schedule Log
	Signed Informed Consent Forms (or location)
5	**UNANTICIPATED PROBLEMS**
	Copies of AESAE reports if not included in CRF
	SAE log for events in non-site subjects
	All SAE reports from other participating sites
	Protocol deviation logs
6	**Blood Product Investigators Brochure**
	AABB Blood Products Transfusion Guide
	Blood Bank Contact Name
	Treatment Assisgnment Group Log (Located in Blood Bank)
	Blood Bank Master Subject Log
7	**LABORATORY**
	Laboratory Name and Contact Address
	Logistic Arrangements with lab for research lab sample processing (if applicable)
	Lab certifications and normal ranges
	Biological specimen sampling, labeling, storing and shipping procedure
	Biological specimen log

	Shipping records (if central lab is used)
	Temperature Logs (for refrigerated storage outside clinical lab area)
8	**MONITORING**
	Monitoring log
	Monitoring reports
	All site visits and study related meetings (sign in sheet, agenda, minutes etc)
	Correspondence
9	**FINANCIAL DOCUMENTS (may be stored in separate location)**
	Clinical Trial Agreement
	Budget
	Financial expenditure records
	Billing statements

10	**Other Documents**
	Completed CRF's (location)
	Study Closure Documentation
	Publications, presentations, manuscripts, etc

Section 13.5 IRB/REB Continuing Review Process

Purpose
The purpose of the document is to outline the procedures involved with IRB/REB modifications and/or continuing review of the PROPPR study.

Scope
These procedures apply to the PROPPR HCCC/HDCC and all participating clinical sites.

References
FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research

Definitions
ICF- Informed consent form
IRB- Institutional Review board
DSMB- Data safety monitoring board
FDA- Food and Drug Administration
HCCC – Houston Clinical Coordinating Center
HDCC- Houston Data Coordinating Center
PI – Principle Investigator
REB – Research Ethics Board
ROC – Resuscitation Outcomes Consortium

Responsibilities
The HCCC/HDCC is responsible for:

- Development and modification of the PROPPR protocol and all related study documents including the informed consent templates
- Distribution UT IRB approved Protocols and amendments, and other study related documents including informed consent templates
- Ensuring that any clinical site IRB/REB-required modifications do not alter the spirit or meaning of protocol procedures or the ICF template language

The clinical site PI and or research coordinator is responsible for:

- Submitting protocol medications and continuing reviews in a timely manner to ensure the study remains open at the clinical site
- Submitting all continuing review IRB/REB correspondence to the HDCC

Procedures

- Local IRB/REB procedures will be followed for submission of protocol amendments and continuing review.
- Clinical site research coordinators will provide the HDCC regulatory documents coordinator with IRB/REB correspondence associated with protocol amendments or continuing review. The HDCC regulatory documents coordinator will log this information into the PROPPR regulatory database for site metrics reporting and monitoring purposes as detailed in chapters 12 and 15 of this manual.

Section 13.6 FDA Audit Procedures

Purpose – The purpose of the document is to outline the steps necessary to effectively prepare for a scheduled FDA audit.

Scope – This document includes information on what information to collect from the Agency prior to the audit, appropriate notifications which need to be made (e.g., Coordinating Center PI's, officials at the University of Texas-Health Science Center, NHLBI-funding sponsor, etc.), and document organization and availability.

References
UTHealth Policy/Procedures - http://www.uth.tmc.edu/orsc/guidelines/fdainspections.html
21 CFR 312: IND regulations (rev.1987)
21 CFR 50: Informed consent (rev.1981)
21 CFR 56: IRB (rev.1981)
21 CFR 314: NDA regulations (rev. 1985)

Definitions –

HCCC	Houston Clinical Coordinating Center
HDCC	Houston Data Coordinating Center
FDA-	Food and Drug Administration
DSMB-	Data Safety Monitoring Board
IND-	Investigational New Drug

Responsibilities –

Agency Auditor(s)	Individual(s) who represent the FDA on official Agency related review of a study (ies) filed under an IND.

Procedure –
Prior to the audit (if date is known), collect and document the appropriate information at the first point of contact with the Agency and follow procedures as outlined below:

1. Obtain the Details of the Audit Visit
   a. Date of notification
   b. Expected date of audit
   c. Expected duration of audit
   d. FDA investigator contact information (name, phone, email, title)
   e. Names of any additional FDA investigators who will be in attendance

2. Obtain the Content of the Audit Visit
   a. Who/what is being inspected (the trial, an investigator, other)?
   b. Why is the inspection being done (**routine, for-cause, follow up to a form 483 or warning letter, other**)?
   c. Does the Agency want specific personnel available and, if so, who/when?
   d. Does the Agency want specific documents available and, if so, what?
   e. Is any information required to be sent to the Agency prior to the visit? If yes, to whom should the information be addressed and when is the expected date?

3. Notify Relevant Parties About the Audit
   a. Notify the HCCC & HDCC, or participating sites if notification is through the coordinating centers.
   b. Notify ROC and the funding sponsor (NHLBI)
   c. Notify the University of Texas-Health Science Center Office of Research who will in turn, notify:

i. The Office of Research Support Committees Manager
ii. The Office of Institutional Compliance Chief Compliance Officer, Institutional Compliance
iii. Office of Auditing and Advisory Services Asst. Vice President

d. Notify the Dean of UTSPH and the Division Director

4. Prepare Accommodations and Documentation
   a. Secure/reserve workspace for the FDA auditor away from other study records and staff.
   b. Ensure FDA audit visit is scheduled with the HCCC and HDCC PI's and Program Managers. These individuals will be available throughout the visit for assistance with questions or follow up to concerns.
   c. Secure non-Networked laptop computers from UT IT department for the auditors to view electronic records if applicable. These records will not be stored on the machine. Requests for specific electronic files will be downloaded to a flash drive and provided to the auditor during the visit. Alternatively, hard copy printouts should be made available upon request by the Agency.
   d. The HCCC/HDCC Program Managers will oversee the inspection and serve as an escort to the auditor. The auditor will not be permitted free access to any hardcopy or electronic files. The program managers will also be the general study contact person for the auditor throughout the visit.
   e. Identify and prepare records that are likely to be included in the audit (or ones that the FDA identified during the call to schedule the visit). **Do not offer information. Always await a specific request to provide information.** These would include the following:
      i. Overview of the Sponsor's personnel and the delegated responsibilities
      ii. Sponsor's Internal SOPs
      iii. Data Management Overview of Web-based Data Entry
         - Data Query and Data Correction Process
         - eCRF Version Control
      iv. Network Security Systems Overview
         - Secured Login Access
         - Audit Trail Process
      v. Screening Logs
      vi. Census Report for Enrollment
      vii. Regulatory Document Storage and Control
         - Protocols
         - Investigator Brochures
         - Informed Consent Forms
         - Protocol Amendments
         - FDA 1571 and FDA 1572s for each center/satellite
         - CVs/licenses/delegation of authority for site personnel
         - Laboratory certification/Laboratory normal ranges
         - Laboratory director CV/license
         - Device accountability logs
         - Sponsor correspondence
         - IRB Information (Federalwide Assurance numbers, Rosters)
         - IRB Submissions and Correspondences for the Sponsor and each center/satellite
         - IND Safety Reports

5. Arrival of the Agency Auditor
   a. The Program managers will greet the Agency auditor and request the individual sign-in (See FDA Inspection Sign-In Page in this SOP).
   b. If not presented by the auditor, the Program Manager will request to see the auditor's credentials to verify that they are in order.

c. The HCCC/HDCC PI(s) will receive the Notice of Inspection (482) from the auditor and will provide the auditor with a brief summary of the relevant study(ies). The HCCC/HDCC PI(s) will also be available each day during the audit to answer questions that may arise.
d. The Agency Auditor will be escorted to a work area that is free of study records, has access to a telephone, and is in a quiet area aware from other employees.

6. Guidance for Responding to Questions from the Agency Auditor
   a. Answer the question that was asked. Be concise.
   b. When uncertain of the answer, defer to others or refer to supporting documents already presented to the auditor.
   c. Be clear, positive, and confident
   d. When indicating a corrective action, only commit to what you can deliver.
   e. Do not volunteer information
   f. Do not guess, speculate, lie, or argue
   g. Do not panic
   h. Do not sign affidavits

7. Providing Documents to the Agency Auditor
   a. Provide only documents that are specifically requested.
   b. Any copies that are made and provided to the Agency Auditor should be stamped "**confidential**" and a copy maintained by the Sponsor (to serve as a record of what was provided to the Agency).
   c. If photographs are taking by the Agency Auditor, duplicates should be taken at the same time by the Sponsor (for records).

8. Exit Interview with Agency Auditor
   a. Should be attended by the HCCC/HDCC PI's and Coordinating Center Program Managers, a representative from the University of Texas-Institutional Compliance Office, and any other appropriate members of the project team.
   b. Following the Agency Auditor's review of any noted deficiencies, the Program Managers will seek to correct any errors in the findings and will reach a point of clarification with the Agency Auditor.
   c. Observations, comments, and commitments will be recorded.
   d. If a Form 483 is issued by the Agency, the HCCC/HDCC PI's will draft a response and forward it to the University of Texas Institutional Compliance Office. The HCCC/HDCC PI's will also submit the written response to the FDA and to the funding sponsor (NHLBI).
   e. Once the Establishment Inspection Report is available, the Program Managers will forward a copy to the University of Texas Institutional Compliance Office.

FDA AUDIT CHECKLIST

WHEN FDA CALLS TO SCHEDULE A SITE VISIT, OBTAIN THE FOLLOWING INFORMATION[1]:

Call date:		
Starting date:		Expected Duration:
FDA Investigator Contact Information	Name	
	Telephone	
	Title	
Additional FDA Investigators' Names?		

ASK:

Who / what is being inspected? *Wait for specific answers. Do not make suggestions*.		
	Clinical trial(s)/study	Details?
	Principal Investigator Co-Investigator(s)	
	Other	
Why is the inspection being done? *Wait for the answer. Do not make suggestions*.		
	Routine? (i.e. IND)	Details?
	Directed (for cause)?	
	Follow-up (i.e. 483; warning letter ?)	
	Other	
Does the FDA want specific personnel available? no yes →if yes, then list		
Who		When
Does the FDA want specific documents available? (List on separate sheet if needed)		
Does the FDA want any of these documents sent prior to their arrival? no yes →then:		
Address:	How? overnight registered certified	
	Delivery by when?	

IMMEDIATELY,
CONTACT AND SEND NOTIFICATION TO THE FOLLOWING:

- HCCC/HDCC PI's and Program Managers

- ROC PI and Program Manager

At least one week before the scheduled visit, the Research Coordinator should complete the following activities[2]:

Check		Comments
Step 1	Gather and review study documents – detailed list follows	
	Note any problems (e.g. missing or incorrect documents)	
Step 2	Secure/reserve work space for FDA representative away from other study/clinical records and research staff	
	Optional: Contact the Office of Research to reserve audit work space	
Step 3	Coordinate with appropriate affiliate institutions to confirm plans for site visit support	
Step 4	Prepare the following documents:	
	A general overview of the study	
	List of all personnel and delegated responsibilities	

[1] Activity checklist is taken in part from "Pre-FDA Audit Checklist"; Pre-FDA Audit Investigator Site Preparations training class by GA International Donald Ashbrook and Robert Kagon; Nov. 13, 2002.

B. Subjects list		
	(de-identified) List of all subjects enrolled, including site, study number, date enrolled and completed	
C. Current Active Studies		
	List of Principal Investigator's current active studies	
Step 5	**Gather and organize the following documents:**	
A. Organize all Regulatory Files by general heading arranged in chronological order (or reverse chronological order)		
	Protocol, include all versions	
	Investigator's Brochure, all versions	
	Informed Consent Form, all versions	
	Protocol Amendments	
	Form FDA 1572 or Declaration of Investigator (DOI- device studies), all versions	
	CVs for PI and Sub-investigators listed on all versions of Form FDA 1572, DOI	
B. Communications (where applicable)		
	Sponsor Correspondence	
	Medical and Study Monitor Correspondence	
	Monitoring Log	
C. IRB Files		
Note: Pay attention to date of IRB notification and date of IRB acknowledgment and/or approval		
	Approval Letter (initial) for initial protocol with original informed consent	
	Amendment approval(s) with the approved informed consent	
	Approvals for:	
	Periodic or Annual Reports	
	Renewal Documents	
	Notification of:	
	Adverse Events	
	Deaths	
	Acknowledgement of:	
	IND Safety Reports	
	Study Termination	
	Final Summary	
D. Laboratory		
	Laboratory Certification and normal ranges	

Section 13.7 End of Study Procedures & Records Retention

Purpose
To describe the manner in which regulatory documents and other study-related documents are to be maintained at an investigational site and to create a system of record retention that can facilitate document retrieval by Monitors, Quality Assurance Auditors, or FDA inspectors.

Scope
This SOP applies to all PROPPR Clinical Sites and the PROPPR HCCC/HDCC Coordinating Centers personnel. This SOP includes the process and activities related to the retention of clinical study records.

References
21 CFR 312.55 – Informing Investigators
21 CFR 312.57 – Record Keeping and Record Retention
21 CFR 312.58 – Inspection of Sponsor Records and Reports
21 CFR 312.62 – Investigator Record Keeping and Record Retention
21 CFR 312.64 – Investigator Reports
21 CFR 54.4 – Certification and Disclosure Requirements
21 CFR 54.6 – Record Keeping and Record Retention
21 CFR 312.68 – Inspection of Investigator's Records and Reports
21 CFR 56.107 – IRB Membership
21 CFR 56.115 – IRB Records
ICH Guidelines for Good Clinical Practice (E6) section 4.4 – Communication with IRB/IEC
ICH Guidelines for Good Clinical Practice (E6) section 4.9 – Records and Reports
ICH Guidelines for Good Clinical Practice (E6) section 5.22 – Clinical Trial/Study Reports

Definitions
CRF- Case Report Form
EMR- Electronic Medical Record
HCCC- Houston Clinical Coordinating Center
HDCC- Houston Data Coordinating Center
eCRF- Electronic Case Report Form
IND- Investigational New Drug
PI- Principal Investigator
NHLBI- National Heart, Lung, and Blood Institute

Responsibilities
The site Principle Investigator (PI) or designee is responsible for:
1. Receipt, maintenance, storage, and availability of the regulatory documents binder once the study is underway.
2. Storage of all study records in an appropriately secured location for a period specified by institutional policy, state or federal regulations, or for a minimum of at least two years following FDA notification of study completion.
3. After completion of the study, if on-site record storage is impractical; records may be stored in a secure off-site facility provided the records are readily accessible in the event of an audit.
4. In the event the PI leaves the clinical site; the PI is responsible for provide the HCCC/HDCC with written notice of the location of study records and the name and phone number of an alternate contact in the event of an audit.
5. The site PI or designee is responsible for ensuring site personnel are trained on this SOP. Such training will be documented on the site training log.

The Houston Data Coordinating Center (HDCC) is responsible for:

1. Collection, organization, and providing regulatory documents to clinical sites at the outset of the study.
2. Establishing and maintaining a tracking system for the timely update of clinical site regulatory documents.
3. Routine communication with clinical sites on regulatory documents with pending expiration dates and collection of updated documents.
4. Providing centers with a date of destruction for clinical research records, if not otherwise specified by local site policies/procedures.
5. The HCCC/HDCC PIs or designee is responsible for ensuring that all appropriate HCCC/HDCC personnel are trained on this SOP. Such training will be documented on a training log.

Procedures

Regulatory Documents

1. The HDCC will provide clinical site research coordinators with regulatory documents binder templates.
2. The site research coordinators will ensure that the appropriate documents are placed in the regulatory documents binders on a regular basis and maintained in a secured area with restricted access. The research coordinator will make the binders available for review by the monitor at each site visit.
3. The HCCC/HDCC will work with the research coordinator at each center to ensure documents are complete and current.
4. The HCCC/HDCC will keep electronic copies of all documents received by the centers and will keep any hard copies received in a locked and secured area with restricted access.

Source Documents, Consents, and CRFs

1. The research coordinator or delegate will transcribe the appropriate data from the source documents into each subject's case report form for entry into the eCRF.
2. The research coordinator will ensure that all source documents, consents, and CRFs are stored in a secure location with access limited to research team members, (i.e., monitors from one Sponsor/CRO may not see study documents from another study).
3. The method of clinical documentation at each site (i.e. electronic EMR vs. paper clinical record) may necessitate a separate folder of source documents for completion of the CRF.
4. The HDCC study Monitor will review study document security during regularly scheduled site visits.

Contracts and Financial Records

The research coordinator will store contracts, budgets, and infrastructure documents apart from subject records, in a secure location with access limited only to research team members.

Chapter 14 - Patient and Data Confidentiality

Section 14.1 Overview

The design and procedures of the PROPPR study are consistent with the U.S. "Privacy Rule", which regulates the 1996 *Health Insurance Portability and Accountability Act*, as well as the Canadian Federal 2000 *Personal Information Protection and Electronics Document Act*, and the Ontario Provincial 2004 *Personal Health Information and Privacy Act* and the British Columbia *Freedom of Information and Protection of Privacy Act.* In general, these laws reflect the emerging consensus about "Fair Information Practices", which are gaining international acceptance (Guidelines for protection privacy and confidentiality in the design, conduct and evaluation of health research: Best practices (Consultation Draft), March 22, 2004. Ottawa: Canadian Institutes of Health Research. Privacy Advisory Committee: (http://www.cihr-irsc.gc.ca/e/20490.html)

Section 14.2 Confidentiality Procedures

Purpose
To describe the requirements for proper handling and control of sensitive electronic and paper records and data.

Scope
This SOP applies to the PROPPR clinical and coordinating center staff.

References
FDA Guidance for Industry: Electronic Source Documentation in Clinical Investigations, December 2010
University Information Technology Services- IT policy
Research Repositories, Databases, and the HIPAA Privacy Rule
http://privacyruleandresearch.nih.gov/research_repositories.asp
21 CFR 11

Definitions
HCCC – Houston Clinical Coordinating Center
HDCC— Houston Data Coordinating Center
DSMB—Data Safety Monitoring Board
FDA—Food and Drug Administration
NHLBI—National Heart, Lung, and Blood Institute
PHI—Protected Health Information

Sensitive records and data include the following:

- Management information concerning workload, performance, staffing, and similar data.
- Correspondence and documents, which must be protected from unauthorized alteration or disclosure. These types of data include all correspondence, memoranda, and other documents whose release or distribution outside the HDCC needs to be controlled.
- Clinical trial data.
- Payment information that is used to authorize or make cash payments to individuals or organizations.
- Proprietary study related information that has value in and of itself must be protected from unauthorized disclosure.
- Correspondence and documents that are considered highly sensitive and/or critical to an organization and must be protected from unauthorized alteration and/or premature disclosure.

- Records subject to the Privacy Act, which contain information that meets the qualifications for Exemption 6 of the Freedom of Information Act, i.e., for which unauthorized disclosure would constitute a "clearly unwarranted invasion of personal privacy" likely to lead to specific detrimental consequences for the individual in terms of financial, medical, psychological, or social standing.

Responsibilities

- All HCCC/HDCC staff handling sensitive PROPPR records and data are responsible for adhering to the procedures described herein.
- The HDCC PI, Biostatisticians and programming staff has access to the entire database, including sensitive information. The HDCC project manager has restricted access to the database via reports and database views created by the programming staff. The programming and PM teams work together to ensure that data produced for reports or datasets, had been de-identified and blinded (with DSMB oversight exceptions for un-blinded reports).

Procedures

It is the responsibility of the sites to ensure that the HDCC receives only information that has been de-identified (stripped of PHI, listed at the end of this section).

Clinical trial data, related documents, and associated correspondence are received by the HDCC from clinical centers and core labs through a variety of methods. Clinical centers access the database via the electronic data capture system, which is housed on the SPH Network's website. Access to the data entry portal is restricted and password protected with timeout features for inactivity. Additional electronic data are received from the core containing de-identified data prepared for upload into the PROPPR Lab database. Documents containing data or related information are periodically received via fax (e.g., adverse event supporting documentation).

Computers, Fax Machines and Printers

Computers, fax machines and printers that may be used for confidential data shall be placed in secure areas where access is restricted to only those individuals with permission to access confidential information. Sensitive electronic data will be stored on a designated secure server. Storing data on workstations will be minimized wherever possible and deleted immediately. Staff will verify correct fax numbers when sending confidential information, and always use a HDCC fax cover sheet. If an unintended fax that contains confidential information is received, immediately inform the sender and either secure or destroy the information. Staff will stand at public fax machines or printers or have documents containing confidential information retrieved immediately so that unauthorized individuals have no opportunity to see the information. All faxes need to state the confidential nature of the contents of the communication and contain instructions should the fax be misdirected.

Computer Display

- Staff will remove confidential data from screens where it is not required.
- Staff need to be aware of the position of computer screens. Unauthorized individuals should not be able to read screens containing confidential information. Use a monitor visor or hood in service areas.
- Staff need to be sure to log off from applications that show confidential data so that no data is accessible after you are finished.
- Computers that are used to access confidential data will have screen savers so that unauthorized people cannot read the information if they happen to wander into a restricted area.
- Computers that are used to access confidential data will have a time-out feature so that when a staff person steps away from his/her computer for a period of time, the staff person is required to re-enter his or her password.

Telephone, Internet (email) and Other Communications

References to any subject in the PROPPR trial will include only the study ID number. Subject names are considered PHI and should not be used. Staff will not verify a study subject by any identifier other than their study ID. Conversations (between staff members and/or staff and other individuals) containing confidential information must be restricted to 'private' and non-traffic areas where the conversations cannot be overheard by others. When reasonable, move to a private room, move to a corner of a room, keep voices low, etc.

- Staff will avoid discussing confidential information in public spaces such as elevators, lavatories, or break rooms.
- Staff will not leave voice mail messages containing confidential data on voice mail boxes that may be accessed by more than one individual, staff will leave instructions on the voice mail that instructs the caller not to leave confidential information as part of their message.

Paper

- Staff will remove PHI from supporting event documentation where it is not required.
- Paper records and reports containing PHI will not be left in locations where non-PROPPR staff (or others without authority to view the information) have access to that information such as printers or unattended on a desktop in open view. Reports which are no longer needed and contain confidential and/or sensitive data must be shredded or stored securely in a locked file cabinet until they can be shredded.

Passwords

- Computers that are used to access confidential data must be password protected.
- Employees should only be given access to those computers and information to which they are entitled. Each employee must use his/her own user name and password to access computers containing confidential data.

Laptops and PDAs

- Laptops or other portable devices (PDA's, etc.) should not be used to store confidential information.
- Laptops and other portable equipment (PDAs, travel drives, CD/DVDs, etc.) that contain confidential information must be kept secure and able to be accessed only by authorized individuals.
- Staff will delete confidential information from laptops and personal devices as soon as it is no longer needed on those devices.

Storage of confidential information

Staff will store copies of confidential information, such as lab reports and printouts, in locked file cabinets or desks.

Staff will store non-reproducible confidential information in areas designed to safeguard it from unauthorized viewing and damage from natural cause.

Staff will store CDs or travel drives in a locked file cabinet or desk. Media with sensitive information must be locked in a cabinet with a non-standard key lock.

Administrative data will be stored on the network drive rather than physical drive on your PC. Caution should be used when storing administrative information on portable computers.

Staff will regularly back up locally maintained confidential information stored on disks to ensure that information is not lost in the event of disk failure and store backups in a locked facility with limited access.

Staff will protect electronic records containing confidential data, including backups, during storage by encrypting the confidential data.

All confidential information must be protected from cleaning staff, maintenance staff and others who may have a need to access the facility where confidential information is located.

Records and reports (paper and electronic) containing confidential information will be stored in locked rooms, cabinets and/or desks when not in use. Access to these rooms, cabinets and desks will be limited to those who are authorized to access the confidential information.

Employees shall 'clean' their desks of all materials containing confidential information prior to leaving at the end of the day, and store the materials securely.

Access

Staff will ensure that all keys and other items that allow access to confidential information, both physical access and computer access, are returned when the individual's access to the information is no longer appropriate.

Staff will use logs or electronic audit trails to monitor access to records with confidential data.

Staff will ensure all PROPPR consent forms include appropriate HIPAA language.

- names
- geographic subdivisions smaller than a State, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code
- all elements of dates (except year) for dates directly related to an individual (e.g., date of birth, admission)
- telephone numbers
- fax numbers
- electronic mail addresses
- social security numbers
- medical record numbers
- health plan beneficiary numbers
- account numbers
- certificate/license numbers
- vehicle identifiers and serial numbers, including license plate numbers
- device identifiers and serial numbers
- web universal locators (URL's)
- internet protocol (IP) address numbers
- biometric identifiers, including finger and voiceprints
- full-face photographic image and any comparable images
- other unique identifying number, characteristic, or code

Chapter 15 - Site Activity Reports

Section 15.1 Invoicing Requirements

Subagreements between UTHealth and the participating clinical sites indicate that UTHealth will reimburse each subcontractor for the direct and indirect costs incurred in the performance of tasks outlined in each subagreements scope of work. The total costs cannot exceed the estimated cost that is provided in each subagreement.

All subcontractors should submit invoices at least QUARTERLY to UTHealth at the following address:
POST AWARD FINANCE TEAM
The University of Texas Health Science Center at Houston
7000 Fannin, UCT 902
Houston, Texas 77030

Invoices should be submitted:

- using the standard invoice shown at the end of this section
- prepared on entity letterhead
- certify that all payments requires are for appropriate purposes
- state the period for which reimbursement is being requested
- itemize the costs by the following budget categories:
    - Salaries
    - Employee Benefits
    - Equipment
    - Consultant Costs
    - Travel
    - Other Direct Costs
    - Total Direct Costs
    - Indirect Costs
    - Total
- show current costs and cumulative costs to date
- include subaward number
- signed by Subcontractors authorized representative

Final invoice is due no later than 30 days following termination, and it must be signed and marked “Final.” In addition, the final invoice should include the following statement:

> "The Subcontractor assures to the University that all expenditures were incurred in full compliance with OMB Circular A-133 or its own applicable audit regulations. Disallowed costs if found during the retention period of this Subcontract will be promptly refunded to University."

If a finding or questioned cost is found related directly to this Subcontract, then the Subcontractor will promptly notify the University in order to proceed with resolution of such matter, as may be required by University's prime sponsor or applicable Federal regulations.

The following expenditures require prior approval of the University Contract’s Director, Office of Sponsored Projects, or designee:

1. A 25% reduction in time devoted to the project by the Principal Investigator or Project Director.

2. Items of general purpose equipment, e.g., office equipment and furnishings, air conditioning, reproduction equipment, automatic data processing equipment, etc.

3. Individual items of equipment costing $5,000 or more. All such items identified in the budget attachment are automatically approved for acquisition.

4. The subaward, transfer or contracting out of any work except for routine purchase of supplies, materials, equipment or general support services.

Even though The University of Washington is not a subcontractor of UTHealth, it is a clinical site. A detailed report of their expenditures should be sent annually to the PROPPR Financial Administrator, Xiang Fang at Xiang.Fang@uth.tmc.edu.

Annual Financial Reports
In addition to invoicing mentioned above, a separate financial report is due annually by **August 1st** to the HCCC via email (Xiang.Fang@uth.tmc.edu). The financial report should include your estimated expenses and carryover (if applicable) in the current ROC funding year (Jan-Dec) and projected budget for the next ROC funding year.

For sites not currently receiving funding from an HCCC subcontract, a quarterly financial statement with itemized expenses is required in addition to the annual financial report described above.

Below is the PROPPR Study Patient Care Costs Reimbursement Form, which should be completed and attached to the quarterly invoice in order for HCCC to monitor the enrollment and the associated patient care costs.

EXHIBIT D

Sample Invoice

COLLABORATOR:_____ Date: _____

PAYMENT ADDRESS:
_____
_____
_____
_____

INVOICE NO. _____
PRIME AWARD NO. _____
SUBAWARD NO. _____
AWARD AMOUNT $_____

Billing Period:

_____ to _____

Submit invoice to:
Post Award Finance
The University of Texas Health Science Center at Houston
7000 Fannin, UCT 902
Houston, Texas 77030-1500

Description/Cost Items	Amt Billed for Current Period From: To:	Cumulative Amt from Inception From: To:
Personnel		
Consultant costs		
Equipment		
Materials and Supplies		
Travel		
Other Direct costs		
IDC Exclusions		
Indirect cost		
Total costs		

I certify that this request represents a reimbursement of actual costs incurred during the invoice period and that these costs are appropriate and in accordance with this Subaward. The COLLABORATOR further certifies that payment made by UTHSCH under this Subaward shall not duplicate reimbursement of costs and services that are received from other sources.

Signed: _____
Project Director/designated signatory

Approved for payment: _____
COLLABORATOR/authorized financial official

PROPPR Patient Care Costs Reimbursement Form

Subcontractor: _____ Date: _____

Current billing period: _____

Total amount billed for current period: _____

Cumulative amount billed from Inception: _____

	Enrolled Patients in Current Billing Period	**Cumulative Enrolled Patients from Inception**
List Enrolled Patients by Patient Study ID Number		

I certify that all patient care costs reimbursement requested are for appropriate purposes and in accordance with the Subcontract documents.

Signed: _____
Principal Investigator/designated signatory

Section 15.2 Technical Progress Reports

Annual reports are to be created by all clinical sites. These reports will reflect all progress on the project and current budgetary issues. The HCCC will compile these reports and included them as a part of their own annual report. A separate report will be required from the HDCC and will pertain to their activities. The HCCC and HDCC reports are to be emailed to Kellie Sheenen and Judy Powell at ROC at the end of that year. These reports are for internal documentation purposes, but they may be used in the preparation of reports that will be sent to the NIH. They will also serve as a log of clinical and administrative activity related to the PROPPR project. Although only annual reporting is required, it is strongly recommended that all sites continue to compile information on a quarterly basis to minimize workload when preparing the annual report.

Section 15.2.1 Clinical Site Reporting

Annually, each clinical site will submit an Annual Report to the Scientific Editor at the HCCC. All reports are to follow the format outlaid in the template at the end of this section. **Reports are due on the 1st of August** (covering July 1 – June 30)**.** Any issues or concerns can be emailed directly to Angela.Beeler@uth.tmc.edu or Erin.E.Fox@uth.tmc.edu

Section 15.2.2 HCCC Reporting

The HCCC will assemble a master report that will include activity from all active clinical sites. This report will also detail the HCCC administrative activity and Laboratory Core Activity. The Systems Biology Core activity will be disclosed in the University of California-San Francisco report. Reports will be sent to ROC at the earliest availability. Because this report requires the additional administrative burden of inclusion of the clinical sites, more time is required. Ideally, these reports will be completed by September 1st.

Section 15.2.3 HDCC Reporting

The HDCC will assemble and submit an annual report that will include activity for the data coordination. Any administrative or data issues will be raised in this report. The report will be submitted as soon as possible after the close of the financial budgets. Ideally, these reports will be completed by September 1st.

Technical Report for

Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial

Clinical Site

Contractor:

Site Principle Investigator:

Dates:

Budgetary:

Changes to the Personnel list since the previous quarterly report are listed below:

Personnel Role

Will be listed as necessary. Once personnel is listed as added, they do not need to be listed again, unless their % effort changes or they are removed from the grant funding.

Expenditures

Equipment and travel purchases and summaries of other expenditures (total supplies or consultant fees) will be briefly outlined here. Please list actual dollar amounts and ensure that they coincide with the invoices you send to UTHealth.

Subcontracts

If applicable, updated information as to any subcontracts you have (i.e., blood banks, lab centers or hospitals) will be listed here. It will include information on the execution of their contracts, the hiring of personnel and their expenditure summaries

Protocol/Enrollment:

*Protcol and IND updates will be listed here. Once the study is up and going, recruitment will be tracked**

Presentations/Publications:

Please site U01 HL077863-7 on any publication or presentation that is PROPPR related. Any such publication, abstract or other presentation should be listed here.

Communication/Meetings:

Indicate the frequency and type of PROPPR related communication and meetings that have occurred at your center or at another site.

Meetings for this quarter:

Meeting / date	Location	Attended by

Any miscellaneous interaction can be listed or described here.

Other Comments/Updates:

Misc information will be stated here

Section 15.3 Site Performance Report

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Report for:
Site XXXX

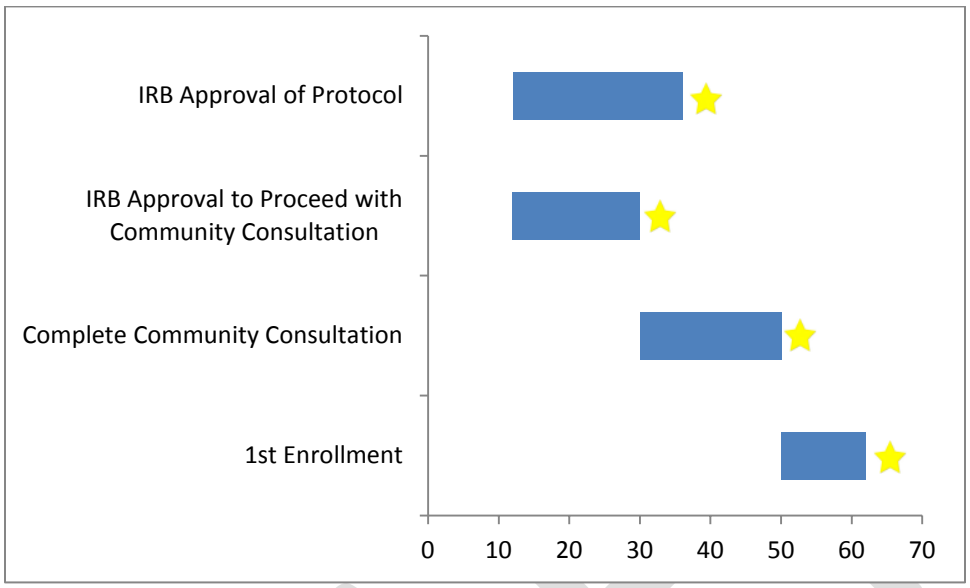
Site Performance Report

July 2012

A Message To Site XXXX

The purpose of this report is to provide you with information concerning your site performance and protocol compliance metrics, HDCC site visit, and data monitoring.

1 Site IRB to Initial Enrollment Performance Metrics



* At day 0, the protocol was received.

2 Protocol Compliance and Data Monitoring Report

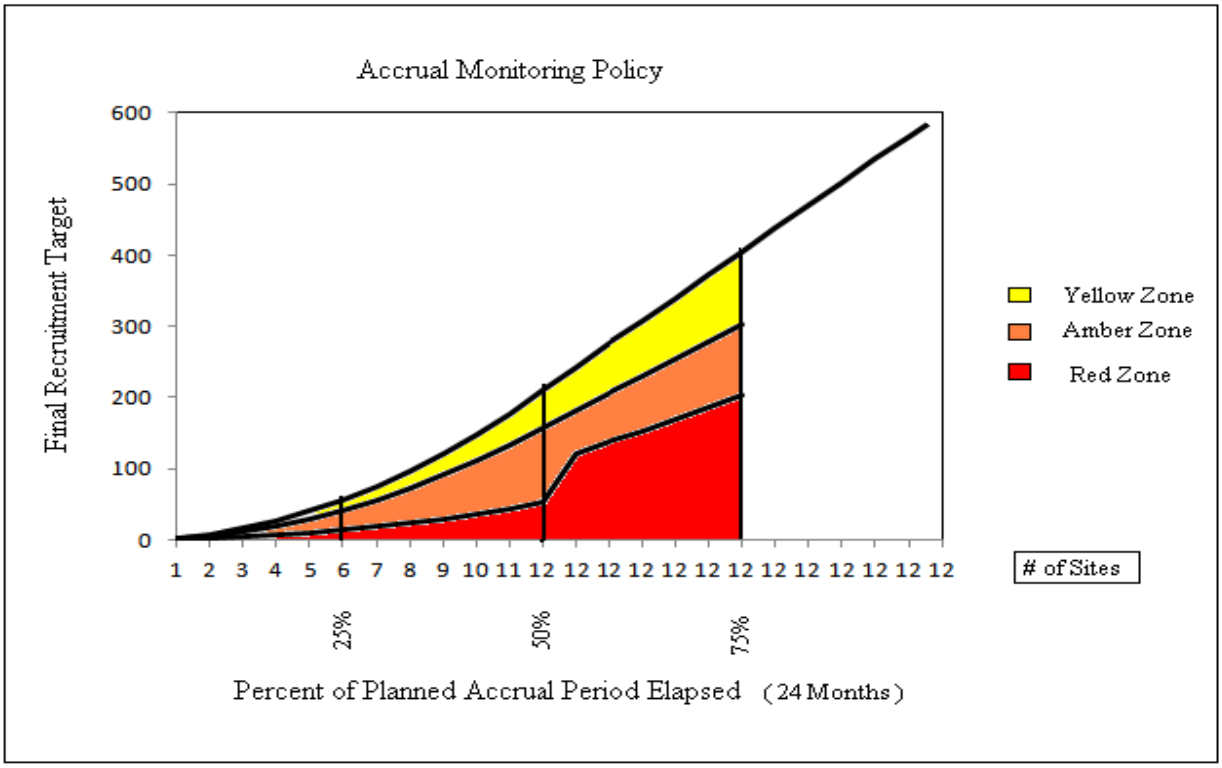


Figure 1. Comparison of Actual to Target Enrollment by Month (for site XXXX)

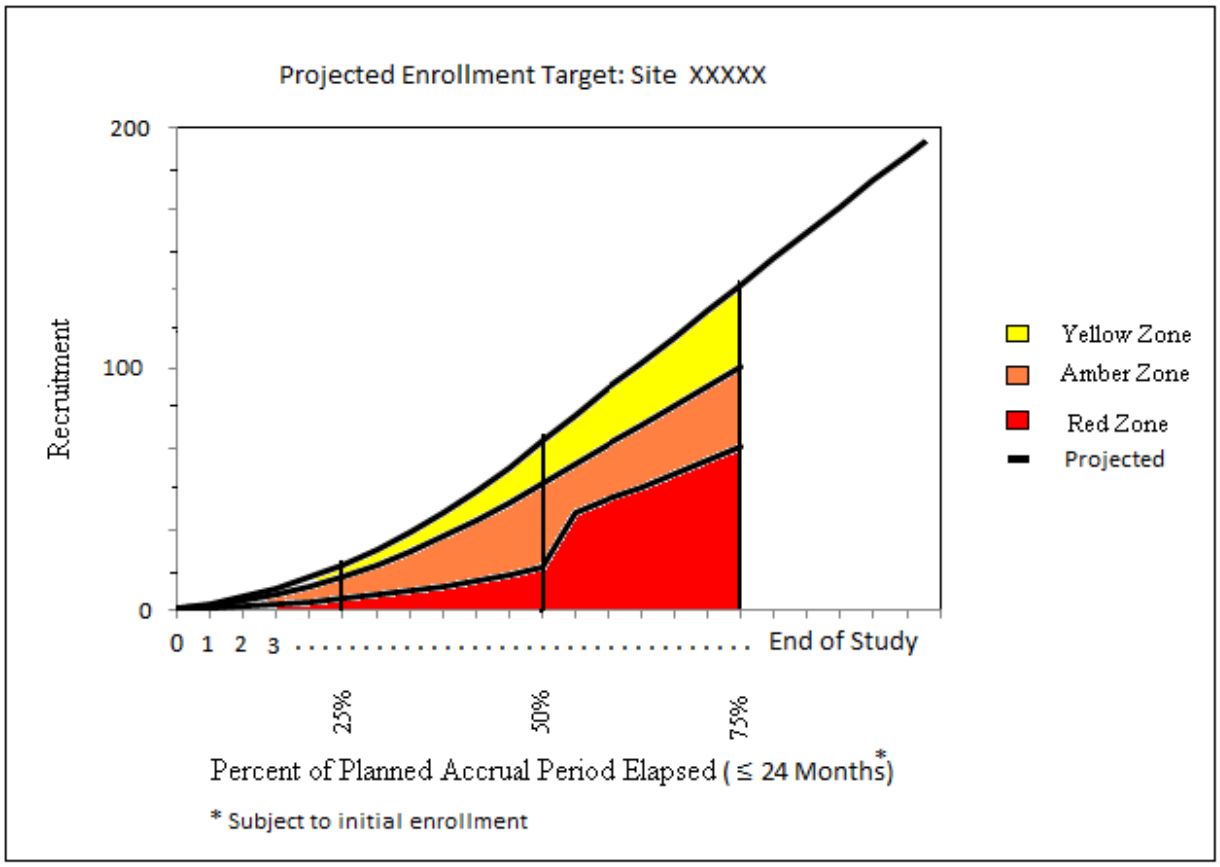


Table 1: Enrollment totals and site percent of total enrollment

Site	Screened (N)	Ineligible		Randomized (n, % of screened)
		Admission Criteria (n, % of screened)	Beyond Two Hours Window (n, % of screened)	
University of Texas Medical School at Houston				
University of California San Francisco				
University of Cincinnati				
Maryland School of Medicine				
University of Southern California – Los Angeles				
University of Arizona				
Medical College of Wisconsin				
University of Washington				
Oregon Health & Science University				
University of Alabama at Birmingham				
University of Tennessee Health Science Center – Memphis				
Sunnybrook Health Sciences Centre				
Overall Totals				

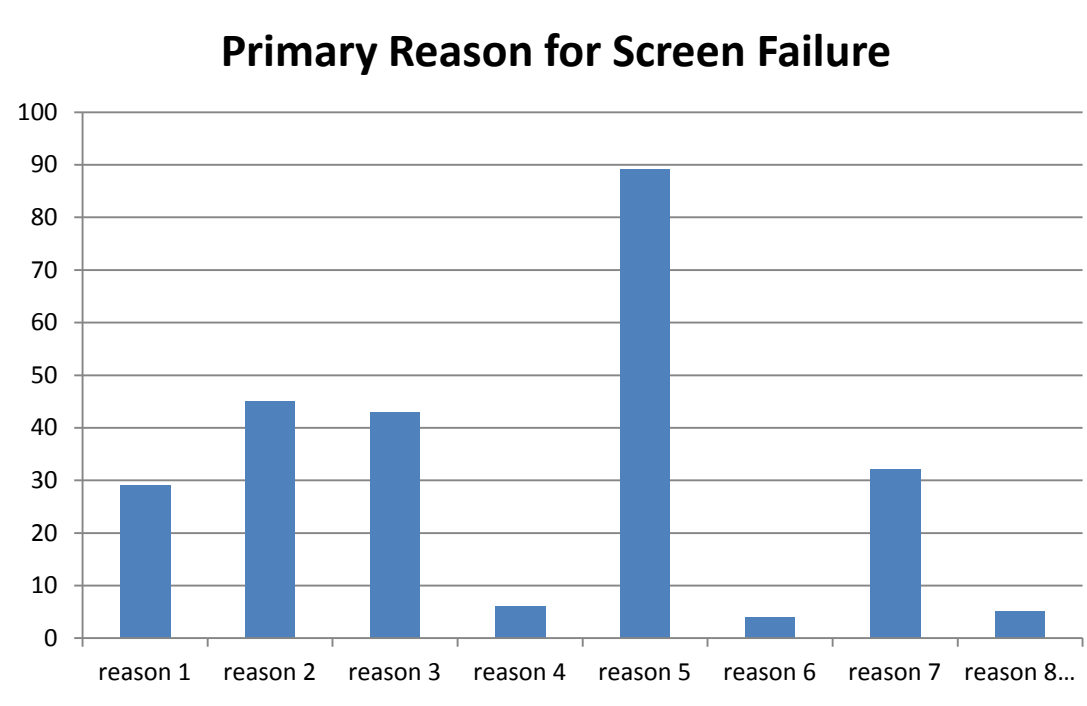

Primary Reason for Screen Failure
100
90
80
70
60
50
40
30
20
10
0
reason 1
reason 2
reason 3
reason 4
reason 5
reason 6
reason 7
reason 8…

Table 2: Process Time measures

Site	Time from Admission to Blood Bank Call (mean, sd, median)	Time from Blood Bank Call to Blood Product Delivery (mean, sd, median)	Time from Blood Product Delivery to Breaking the seal (mean, sd, median)
Subject 1 Subject 2 Subject 3 . .			
Site 1 (mean, sd, median)			
. **.** **.** **.**			
Subject 1 Subject 2 Subject 3 . . **Site 12 (mean, sd, median)**			
Overall sites (mean, sd, median)			

Table 3: Protocol violations

Randomized (n =)	
Type of Violation	**# (# by study monitor)**
Reason 1	
Reason 2	
Reason 3	
Reason 4	
Reason 5	
Reason 6	
Reason 7….	
Total (since last report)	
Cumulative Total	

Table 4: Protocol Deviations

Randomized (n =)	
Type of Deviation	**# (# by study monitor)**
Reason 1	
Reason 2	
Reason 3	
Reason 4	
Reason 5	
Reason 6	
Reason 7….	
Total (since last report)	
Cumulative Total	

Table 5: Volume of data queries

# of CRF Pages Submitted	Queries Issued		Queries Resolved		Days to Resolution	
	N	(%)	N	(%)	Med	Range

Table 6: Missing Case Report Forms

Form	# expected	% completed in window	% completed outside window	% missing
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
Med Watch Death Adjudication Packet				
Total				

Table 7: Adverse and Severe Adverse Events Management

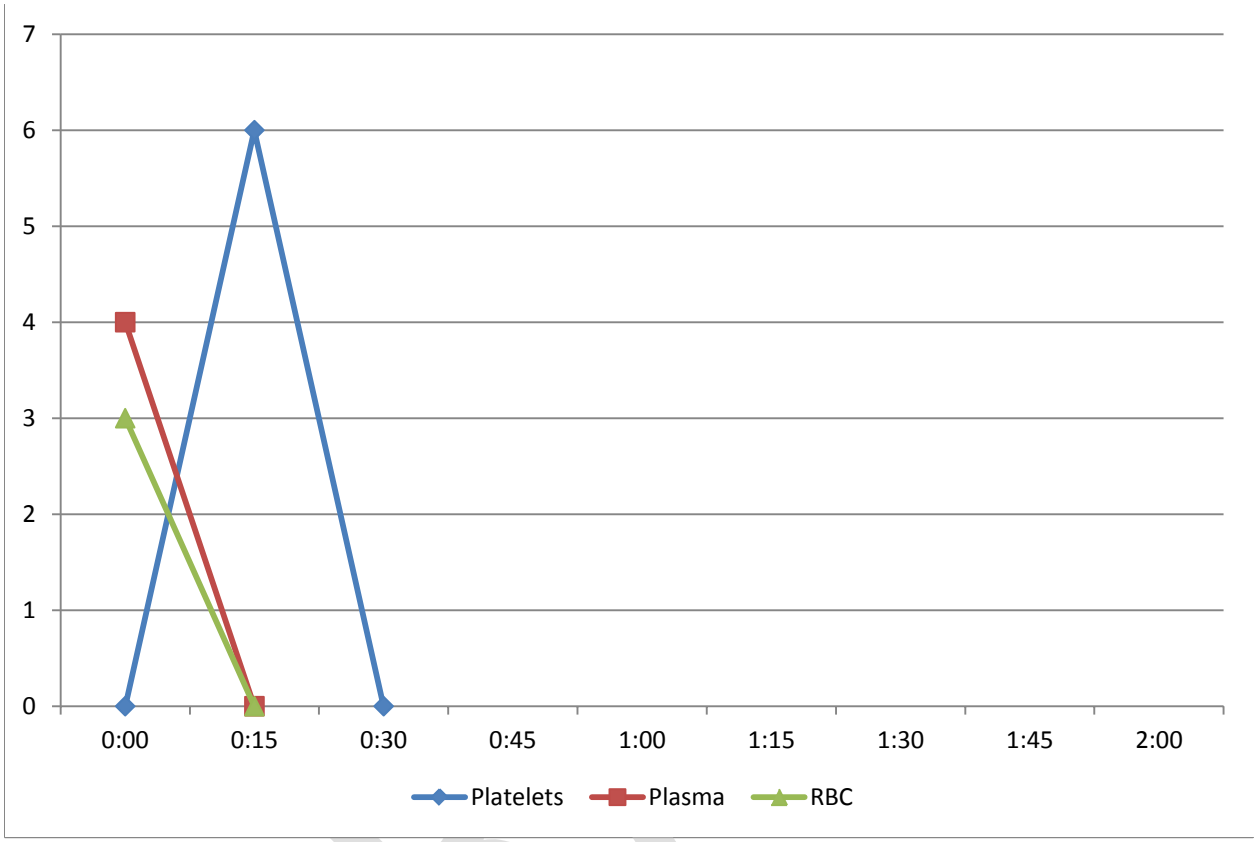
	Total # reported
AE	
SAE	
Total (since last report)	
Cumulative Total	

Table 8: Site Quality and Compliance with Lab Procedures

Laboratory Procedures	Total # of samples required (N)	# of issues	% of subjects with issues *
Collection issues			
Sample not collected			
Improper labeling			
Equipment failure			
Sample mishandled			
Shipping Issues			
Sample not received			
Sample arrived outside of expected time window			
Sample arrived in unusable state			
Total			

* Percents may not add to 100% as a sample may have more than one issue.

Figure: PROPPR Blood Product Transfusion Record



3 HDCC Site XXXX Visit Report

- Initiation visit reports
  - Flowchart (TQI plan)
  - Site specific accommodations

- Any subsequent monitoring site reports

Chapter 16 - Administration and Data Entry

Section 16.1 Overview

Data will be collected using standardized case report forms. After data collection, the data will be entered into a web-based data system designed for this trial. The web site uses encryption technology for data security. Access to the web forms requires an electronic signature and valid username and password; users at a site must be authorized by the site's principal investigator.

Section 16.2 Data Queries

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Checks will be developed by both clinical and laboratory investigators. Depending on the question, any item found that does not meet the respective edit criteria will have an appropriate error message displayed when the user tries to save the data. Errors will be classified as either "hard" errors meaning that a valid response is required before the data can be saved or as "soft" errors in which the entry operator can either correct the errors or override them to indicate that the data are correct although it does not meet the edit criteria. Examples of hard errors would be items such as identifiers and event dates. An example of a soft error would be values that are outside a pre-defined range. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are currently four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors. For the first status, the entry user will have the option to save a record as "incomplete" for situations where they have partially entered a form and must stop because of an interruption. This will allow the user or the study coordinator to pull up the form at a later time and finish completing it. If the form was entered without any errors, then the record will be saved as complete. If the user overrides any soft errors found, the record will be saved as "saved with errors". Staff in the HDCC will have web-access to listings of subject specific errors needing correction by site. These errors can be corrected at the site or in the offices of the HDCC (given documentation of the change). All site investigators will be trained to follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once a follow-up about any errors has been done by the HDCC and the error has been corrected or certified as accurate, the status will be change to "complete with errors." Once a record has been saved by the site or HDCC as complete, they will no longer be allowed to make changes to the records. Any changes that result from obtaining new information would be made by the staff at the HDCC. At the end of the trial after all possible corrections are made, the database will be locked and further changes will not be made.

Since there are times when data does not meet the required edit criteria such as out of range values, the sites still need to be able to save their data. However, such errors need to be followed up to ensure that the error was not by mistake. In this case, any soft error indicated will be logged to an error log data table through which the clinics can later generate a report of these errors that must be followed up on. This report will include the option for the clinic user to enter the correct value(s) if the record was saved by mistake or to indicate that the value saved was

correct in which case they must provide an explanation as to why the error was overridden. These reports must be transmitted back to the HDCC where staff will process the corrections through an error log management system. This process is particularly important for clarifying missing data. Once these reports are received back by the HDCC staff and processed, the respective data record will be updated to the forth status of "complete with errors." Since clinical staff must sign these reports, these reports will serve as audit records should the funding agency need to investigate the process.

Section 16.3 Forms Completion and Data Entry

Section 16.3.1 PROPPR SharePoint and e-CRF OpenClinica Assess

Purpose
To outline the process for allowing clinical site access to the PROPPR Regulatory SharePoint and e-CRF OpenClinica websites.

Scope
This SOP applies to the PROPPR HCCC/HDCC and all clinical sites who have access to the Regulatory SharePoint and e-CRF OpenClinica websites.

References
FDA Guidance for Industry: Electronic Source Documentation in Clinical Investigations, December 2010
FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007
General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002

Definitions
N/A

Responsibilities
It is the responsibility of clinical site PI's, co-investigators, research coordinators, research assistant, and designated data entry or administrative staff to access the PROPPR Regulatory SharePoint website to download Protocol Documents, CRF's, study tools, references, meeting agendas and minutes, and/or review other study related information.

It is the responsibility of the PROPPR Regulatory Documents Coordinator to receive and review electronic signature agreements, and to communicate receipt with the HDCC Senior Programmer Analyst III.

It is the responsibility of HDCC Senior Programmer Analyst III to assign user ID's security profiles.

Procedures
1. All persons who plan to enter data must complete and electronic signature agreement (see document below).

2. Password protected access is granted by the HDCC Senior Programmer Analyst III in consultation with the coordinating center program managers and PI's.
3. File and specific page access is controlled by software protocols related to the assigned user security profile.
4. Real-time checks and balances will occur as data is entered using software programming with defined data parameters.

UTHealth™
The University of Texas
Health Science Center at Houston
School of Public Health
Division of Biostatistics

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

ELECTRONIC SIGNATURE AGREEMENT

This Agreement is between you and the Resuscitation Outcomes Consortium (ROC), Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Study, Houston Data Coordinating Center (HDCC), and provides for your informed consent to use your designated user name and password as an "Electronic Signature". You have registered as a member with the HDCC for the purpose of participating as a coordinator or investigator. The HDCC has created an electronic data transmission system for all clinical forms and requires the use of Electronic Signatures. The HDCC believes that this system reduces the time and expense of data submission and facilitates efficient and accurate data transmission from a clinical trial site to the HDCC, without compromising data integrity, or the rights of the parties. Therefore:

1. You agree that the use of your user name and password constitutes your Electronic Signature when submitting or transmitting documents or data via the internet PROPPR Regulatory and OpenClinica websites.

2. Your Electronic Signature shall be considered for all such purposes as equivalent to your handwritten signature, provided below.

3. Your Electronic Signature, used in accordance with this Agreement, shall have the same legal weight associated with that of an original signature.

4. You agree not to raise the use of an Electronic Signature as a defense in connection with an internet PROPPR website transmission, if your Electronic Signature is used in accordance with this Agreement.

5. Because the combination of your user name and password constitutes your Electronic Signature and bears the same legal weight associated an original signature when engaged in transmissions via the PROPPR Websites, you understand that you are entirely responsible for maintaining user name and password confidentiality. You are accountable for any and all activities that occur using your user name and password. You agree to notify the HDCC immediately of any unauthorized use of your user name or password, or any other breach of security known to you.

6. You agree to notify the HDCC when you leave your position as a PROPPR member in order for the HDCC to deactivate your Electronic Signature.

YOU REPRESENT THAT YOU HAVE READ THIS AGREEMENT. YOU UNDERSTAND THAT YOU ARE AUTHORIZING ALL FUTURE DATA TRANSMISSIONS BY YOU TO BE MADE ELECTRONICALLY VIA THE INTERNET PROPPR WEBSITES AND THAT SUCH ELECTRONIC SUBMISSION CONSTITUTES YOUR ORIGINAL SIGNATURE. YOU AGREE THAT YOUR FACSIMILE SIGNATURE ON THIS DOCUMENT, SHALL BE DEEMED TO BE, AND MAY BE RELIED UPON AS, AN ORIGINAL SIGNATURE.

Please print this agreement, sign and date where indicated below, and return to the PROPPR HDCC by fax at **(713) 500-9530**, or by e-mail to: proppr@uth.tmc.edu.

_____	_____	_____
Printed Name	Signature	Date

_____
Principal Investigator Signature (witness)

Section 16.3.2 Data Entry into the e-CRF

Purpose
To outline the process for training PROPPR clinical site personnel to enter data into the web-based electronic case report forms (e-CRF) database.

Scope
This SOP applies to all PROPPR personnel who enter data in the web-based e-CRF database application.

References
FDA Guidance for Industry: Electronic Source Documentation in Clinical Investigations, December 2010
FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007
General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002

Definitions
HDCC – Data Coordinating Center
CRF – Case Report Form
e-CRF – electronic Case Report Form

Responsibilities
It is the responsibility of the HDCC Program Manager to schedule and perform webinars to train the site personnel on how to enter data into the e-CRFs.

It is the responsibility of the site personnel to attend as many training sessions as necessary until they are aptly able to use the web-based e-CRF system.

It is the responsibility of the site personnel to contact the HCCC/HDCC Program Managers with questions concerning the use of the e-CRF web-based application, including screen prints related to technical difficulties experienced.

It is the responsibility of the HDCC Program Manager to coordinate with the DCC programming staff to resolve site personnel inquiries related to the operation and functioning of the web-based application.

Procedures
A coordinator training meeting will held at the HDCC prior to initiation of enrollment. Clinical site personnel will be given detailed instructions on completion of the PROPPR paper CRF and an overview of the e-CRF web-based data entry application for common and protocol-specific procedures.
Webinars on e-CRF data entry procedures will be provided and recorded for later viewing. The webinars will include:

1. Instructed on how to enter a new patient, how to select a previously enrolled patient, how to navigate to forms from the menu,

2. Instructions to complete at least 2 mock subjects, one randomized and one screening failure, per site in the e-CRF test database,
3. Coordinators will be encouraged to spend time practicing entering new patients, selecting enrolled patients, and entering forms in the test environment before they enroll their first patient to a study.

The HDCC Program Manager will present webinars to provide additional training on using the e-CRF web-based data entry application as needed until staff are aptly able to use the program. These webinars are also held as new personnel or sites become part of the PROPPR Clinical Trial. Focused instruction webinars that cover specific e-CRFs and other targeted topics for training will be scheduled ad hoc and upon request by the PROPPR clinical sites.

Section 16.3.3 Database QA Procedures Using Edit Checks

Purpose
To outline a process for checking the accuracy of data entered into the PROPPR e-CRF.

Scope
This standard operating procedure (SOP) applies to all clinical trial personnel involved in data entry and QA procedures, including research coordinators, HDCC PI, Biostatisticians, programmer analysts, and the program manager.

References
FDA Guidance for Industry: Electronic Source Documentation in Clinical Investigations, December 2010
FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007
General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002

Definitions
eCRF – electronic case report form
Database – a collection of tables that house project data
HDCC – Houston Data Coordinating Center
HDCC PI – Houston Data Coordinating Center Principle Investigator

Responsibilities
It is the responsibility of the programming staff to design and create databases and database objects that meet the needs of the PROPPR study and to conform to good coding practices.

It is the responsibility of the clinical site research coordinators and data entry personnel to resolve data queries within the e-CRF, or at the response of the HDCC or study monitor.

It is the responsibility of the HDCC project manager to review data query reports and process them in the database.

Procedures
Once the research coordinator clicks “Submit” on an e-CRF form, various processes are started. The data fields are initially checked for required fields and appropriate data types. If those conditions have been met satisfactorily, the ranges of the data are checked.

Many data fields have two range checks, a hard error range and a soft error range. The hard error range is the larger range. It is meant to notify the research coordinator of impossible values (e.g., a systolic blood pressure that is negative or zero) most likely occurring when there has been a keying error of the entry. The database does not accept these entries, and the research coordinator must correct the entry before they are allowed to submit the form.

The soft error range checks for unlikely values, generally outside the boundaries for the patient population, though not impossible. An error message flag will appear on the form declaring that an entry is outside of the soft range (and gives the range in the message). The intent is for the data entry person to double check what they have entered and to change the entry if it is in error. If the entry is correct, the data entry person will click “Verify”, and the record will be entered into the database. The record will be given a status of “pending errors”, which mean data queries exist for this record.

The HDCC program manager will monitor pending data errors by site and communicate with the research coordinator. Data corrections will be primarily made with the e-CRF and audit tables will capture all changes to the database

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

PROPPR Study Site Personnel & Responsibility Log

NAME	INITIALS	JOB TITLE	RESPONSIBILITY CODE(s)	START DATE ON STUDY	END DATE OFF STUDY	SIGNATURE
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	

Site PI Signature at Beginning of Study : _____ Date Signed: _____
Site PI Signature at End of Study: _____ Date Signed: _____

Responsibility Codes: **1**. Overall Responsibility for Organization & Conduct of Study **2**. Responsible for Regulatory/IRB Submissions **3**. Recruits Subjects
4. Obtains Informed Consent **5**. Medical Review of all Lab & Clinical Data for Potential AE/SAE's **6**. Processes/Ships Research Blood Samples
7. Randomizes Subjects **8**. Fills Out CRF's **9**. Performs Data Entry into OpenClinica **10**. Submits MedWatch 3500 Safety Reports
11. Performs 30 Day Follow-up Assessment

PROPPR

PROPPR Site Visit Log:

Date(s) of Visit	Purpose of Visit (i.e. initial,training, routine, close-out, ect.)	Print Name	Signature

Section 16. . Equipment Accountability Log

PROPPR

PROPP Equipment Accountability Log Site:

Equipment Description	Quantity Recevied	Date Received	Received By (Initials)	Serial Number (if appicable)	Date Returned	Quantity Returned	Comments
Motorola Barcode Reader							
Motorola Barcode Reader							

Version Date: 2012 FEB 28

Page __ of __

Chapter 17 - Training

Section 17.1 Overview Guidelines for Training Site Personnel

A. Clinical Research Staff Training

All clinical research staff involved with PROPPR must be trained to:

1. Screen all eligible patients
2. Assess the potential patient utilizing the ABC score and communicate with trauma attending regarding the gestalt decision
3. Understand the institution's massive transfusion (MT) activation process
4. Understand the process to notify the blood bank and activate the randomization process
5. Identify the study cooler upon arrival to the patient's bedside
6. Assist with ensuring the study blood products are administered in the correct order according to ratio group
7. Complete "direct observation" and daily data collection forms
8. Knowledgeable about the research sample collection and process
    a. Timepoints for research sample collection
    b. Labeling the tubes (Section 11: Laboratory Manual of Procedures)
    c. Institution specific instructions on how to process the samples during and after normal business hours

B. Physician Training

All trauma, emergency medicine, anesthesiology and transfusion medicine physicians should be informed of the PROPPR protocol:

1. Understand the importance of randomizing the patient early
2. Understand the process of screening for potential patients (utilizing the ABC score or physician override)
3. Understand the importance of the compliance of the administration of the study products once the seal is broken on the 1st container
4. Understanding the purpose of the research lab samples AND understanding that the research samples results will not be used for clinical decisions
5. Understand the definition of hemostasis to determine when the PROPPR protocol will be stopped
6. Be aware of how to administer other agents (i.e. Factor VII, crystalloids, colloids, etc.)

C. Blood Bank Personnel

All personnel in the blood bank must be trained to:

1. Follow the randomization process at the time a patient is to be randomized
2. Understand how to document the randomization number assignment once the seal has been broken
3. Understand how to prepare the containers (especially the 1st cooler with seal and sham product for the 1:1:2 group)
4. Understand the process for notification when seal has been broken – research person to contact blood bank person
5. Understand the process for being notified when the PROPPR MT protocol has been stopped (receive call and the study container is returned to blood bank)

D. Clinical Staff Training

Inservices need to be included for all clinical staff who may be involved in the care of the PROPPR patients (i.e. ED, OR, IR, ICU, floor, etc.):

1. Understand the purpose of PROPPR
2. Understand the process of screening for potential patients (utilizing the ABC score or physician override)
3. Understand the importance of the compliance of the administration of the study products once the seal is broken on the 1st container
4. Understanding the purpose of the research lab samples AND understanding that the research samples results will not be used for clinical decisions
5. Understand the definition of hemostasis to determine when the PROPPR protocol will be stopped
6. Be aware of how to administer other agents (i.e. Factor VII, crystalloids, colloids, etc.)

E. Lab Personnel

Lab personnel who will be involved in the processing of the research samples must:

1. Know how to do the TEG and multiplate processing and reporting
2. Be aware of how to process the remaining research tubes which includes labeling, pipetting into appropriate cryovials
3. Understand how to prepare the samples for shipment
4. Please refer to Chapter 18, Laboratory Manual of Procedures for specific training requirement

F. Tools to use for training

1. Power point presentation (See Section 1.6)
2. "Mock" patient screening and randomization – practice the process when a potential patient is identified and go through how the research staff will screen, randomize, and enroll the subject as well as enter data and collect samples
3. Hand outs – one page summary (Attached at the end of this section)
4. Laminated cards
5. Any other tools, handouts that will be useful for continual education

G. Recommendations

1. Recommend frequent and ongoing training prior to and throughout subject enrollment
2. Monitor each individual's performance on a regular basis and retrain as needed
3. Document attendance at training meetings – use training log to document names, signatures, date of training
4. Remember to train new residents and staff at the beginning of each rotation change
5. Provide updates to all people involved following the patient's enrollment – let them know the positives and negatives of the process and how to adjust

One page summary

Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)
Abbreviated Overview

STUDY DESIGN:
Phase III multi-center, randomized, 2-groups (Massive Transfusions)

STUDY GROUPS:
Group 1 - 1:1:1 ratio of platelets:plasma:RBCs (Platelets given first)
Group 2 - 1:1:2 ratio of platelets:plasma:RBCs (Platelets given first as supplied in containers)

INCLUSION CRITERIA:
>15yr of age
Received at least 1 unit of blood within 1st hr of arrival or prior
Predicted to receive Massive Transfusion: BP < 90, HR > 120, penetrating injury, Positive FAST, surgical discretion

EXCLUSION CRITERIA:
Received care from outside facility, Moribund patients with devastating injuries, Pregnant, >20% BSA burns, Suspected inhalation injury, > 5min CPR, Another interventional study, Opt-Out, LAR refused consent

CONSENT PROCESS: “Exception for Informed Consent”

SCREENING/RANDOMIZATION:
Contact Blood Bank; Container Sent; When Seal Broken , pt is enrolled; if blood products not needed/seal not broken, sent back and randomization number used for next patient

LAB SAMPLE COLLECTION:
0 (admission), 2, 4, 6, 12, 24, 48, 72hrs [4-5 tubes, 20cc each time]

Section 17.2 e-CRF Data Entry Training

Purpose
To outline the process for training PROPPR clinical site personnel to enter data into the web-based electronic case report forms (e-CRF) database.

Scope
This SOP applies to all PROPPR personnel who enter data in the web-based e-CRF database application.

Definitions
HDCC – Data Coordinating Center
CRF – Case Report Form
e-CRF – electronic Case Report Form

Responsibilities
It is the responsibility of the HDCC Program Manager to schedule and perform webinars to train the site personnel on how to enter data into the e-CRFs.

It is the responsibility of the site personnel to attend as many training sessions as necessary until they are aptly able to use the web-based e-CRF system.

It is the responsibility of the site personnel to contact the HCCC/HDCC Program Managers with questions concerning the use of the e-CRF web-based application, including screen prints related to technical difficulties experienced.

It is the responsibility of the HDCC Program Manager to coordinate with the DCC programming staff to resolve site personnel inquiries related to the operation and functioning of the web-based application.

Procedures
A coordinator training meeting will held at the HDCC prior to initiation of enrollment. Clinical site personnel will be given detailed instructions on completion of the PROPPR paper CRF and an overview of the e-CRF web-based data entry application for common and protocol-specific procedures.

Webinars on e-CRF data entry procedures will be provided and recorded for later viewing. The webinars will include:

- Instructed on how to enter a new patient, how to select a previously enrolled patient, how to navigate to forms from the menu,
- Instructions to complete at least 2 mock subjects, one randomized and one screening failure, per site in the e-CRF test database,
- Coordinators will be encouraged to spend time practicing entering new patients, selecting enrolled patients, and entering forms in the test environment before they enroll their first patient to a study.

The HDCC Program Manager will present webinars to provide additional training on using the e-CRF web-based data entry application as needed until staff are aptly able to use the program. These webinars are also held as new personnel or sites become part of the PROPPR Clinical Trial. Focused instruction webinars that cover specific e-CRFs and other targeted topics for training will be scheduled ad hoc and upon request by the PROPPR clinical sites.

Section 17.2.1 e-CRF Data Entry PowerPoint Slides

PROPPR

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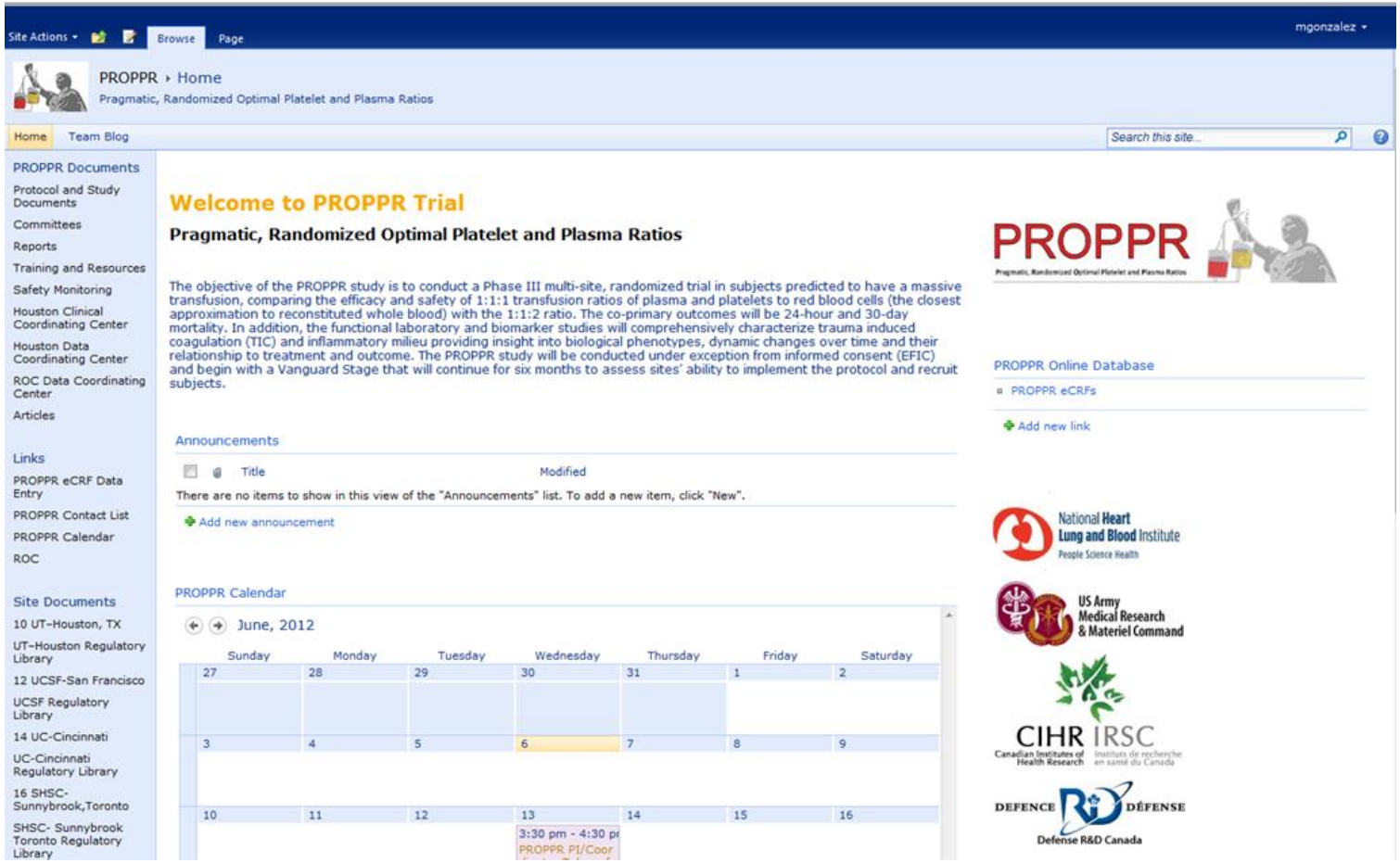
PROPPR Online Database Training

PROPPR Online Database - Access

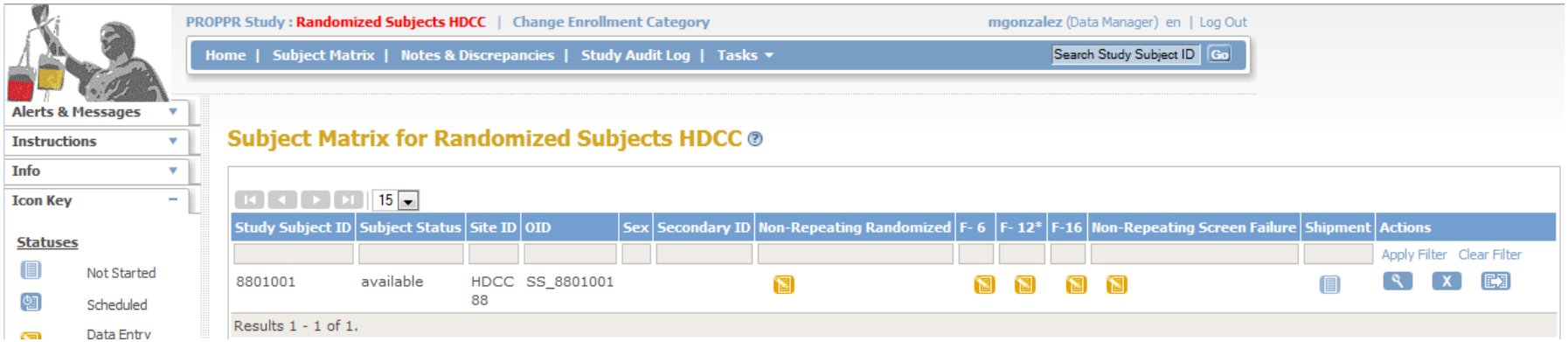


- Access to the PROPPR Online Database can be gained through the PROPPR SharePoint site, using the **PROPPR eCRF Date Entry** link.
- Access can also be gained using a direct link

PROPPR Online Database Login Screen

- Once at the homepage, the user must supply a username and password.
  - Both the username and password are **case sensitive**
- Click the Login button to enter the site.
- If you forget your password, contact the HDCC for password recovery.

Log Out of PROPPR Online Database



- The Log Out button is located on the right hand corner above the Navigation Bar, on the home page.
- To Log Out, click once on the Log Out button and close your browser

PROPPR

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PROPPR Online Database

CREATE A SCHEDULE

PROPPR Online Database Create Schedule

- You can also click once on “Need a Schedule?”, to create a schedule of the eight time points that are used in the PROPPR study. The schedule is created using the admission date and time of the Subject.

PROPPR Online Database Create Schedule

Login

Request Schedule

Please enter admission/ED arrival date and time. The scheduled will be provided for you.
Date format is DD-MMM-YYYY. Time format is HH:MM in 24 hr clock. Please select date from the calendar.

All fields are required. *

Admission Date/Time: 02-Jul-2012 6 : 7

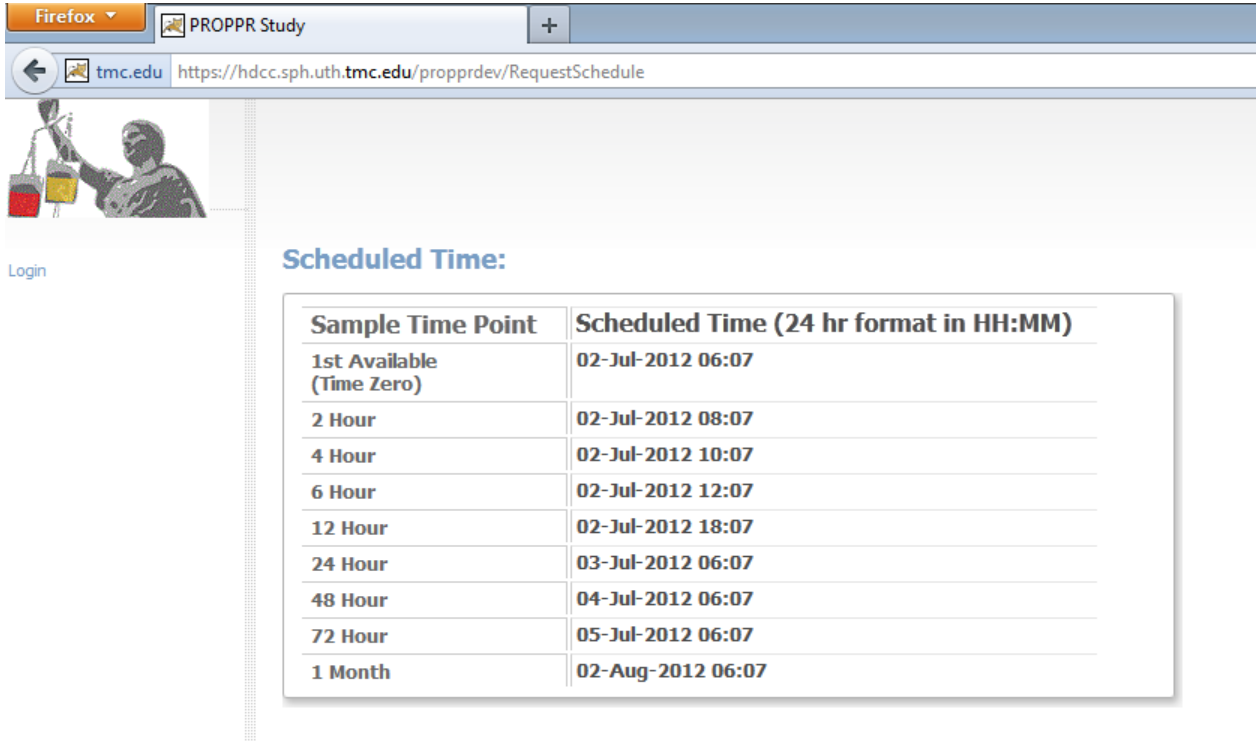
Submit Request Cancel

Scheduled Time:

Sample Time Point	Scheduled Time (24 hr format in HH:MM)
1st Available (Time Zero)	02-Jul-2012 06:07
2 Hour	02-Jul-2012 08:07
4 Hour	02-Jul-2012 10:07
6 Hour	02-Jul-2012 12:07
12 Hour	02-Jul-2012 18:07
24 Hour	03-Jul-2012 06:07
48 Hour	04-Jul-2012 06:07
72 Hour	05-Jul-2012 06:07
1 Month	02-Aug-2012 06:07

- Enter the admission date and time from the provided calendar and drop down lists. Click once on Submit request and the schedule will be created based on these values.
- Once you are ready to Login to PROPPR Online Database, click once on Login to return to the Login page.

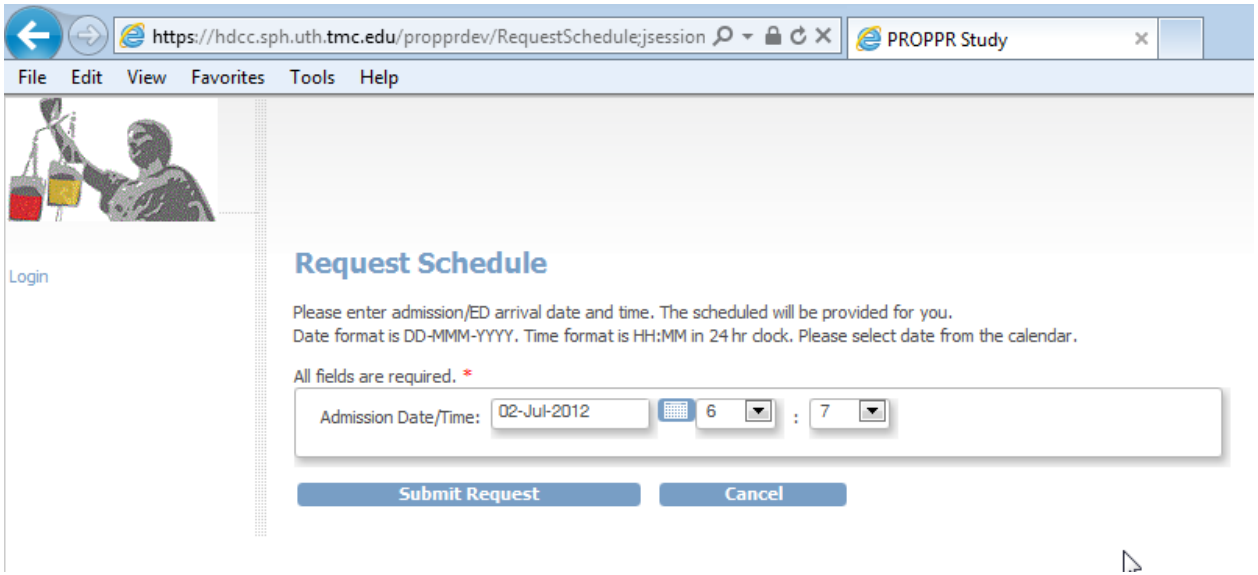
PROPPR Online Database Create Schedule



Sample Time Point	Scheduled Time (24 hr format in HH:MM)
1st Available (Time Zero)	02-Jul-2012 06:07
2 Hour	02-Jul-2012 08:07
4 Hour	02-Jul-2012 10:07
6 Hour	02-Jul-2012 12:07
12 Hour	02-Jul-2012 18:07
24 Hour	03-Jul-2012 06:07
48 Hour	04-Jul-2012 06:07
72 Hour	05-Jul-2012 06:07
1 Month	02-Aug-2012 06:07

- To Print the schedule In FireFox:
- Click on the Firefox menu
- Point cursor to Print option
- Click once on Print
- A copy of the schedule will print.

PROPPR Online Database Create Schedule



- To Print the schedule from Internet Explorer:
- Click on the File
- Click once on Print

Or

- Use the keyboard shortcut: Ctrl+P to print
- A copy of the schedule will print.

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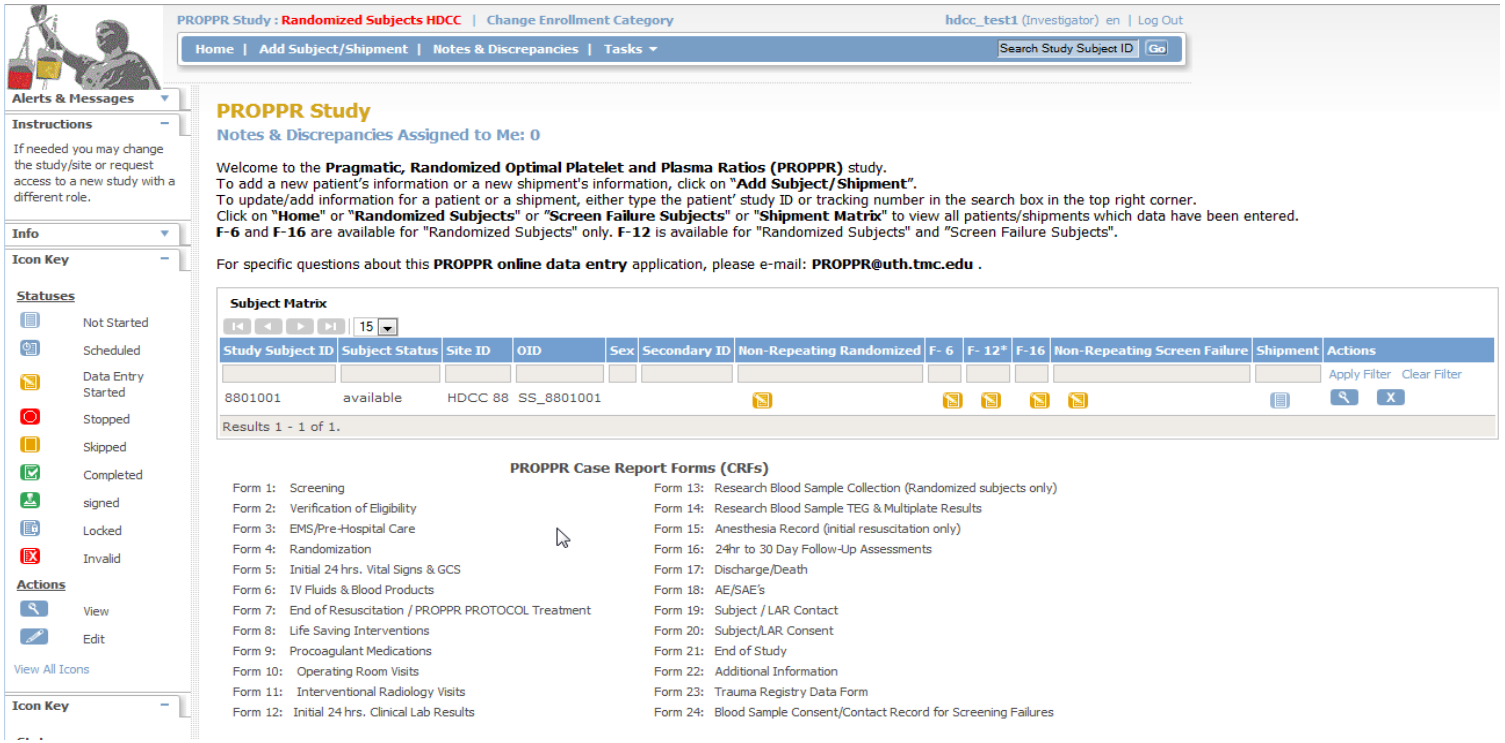
PROPPR Online Database

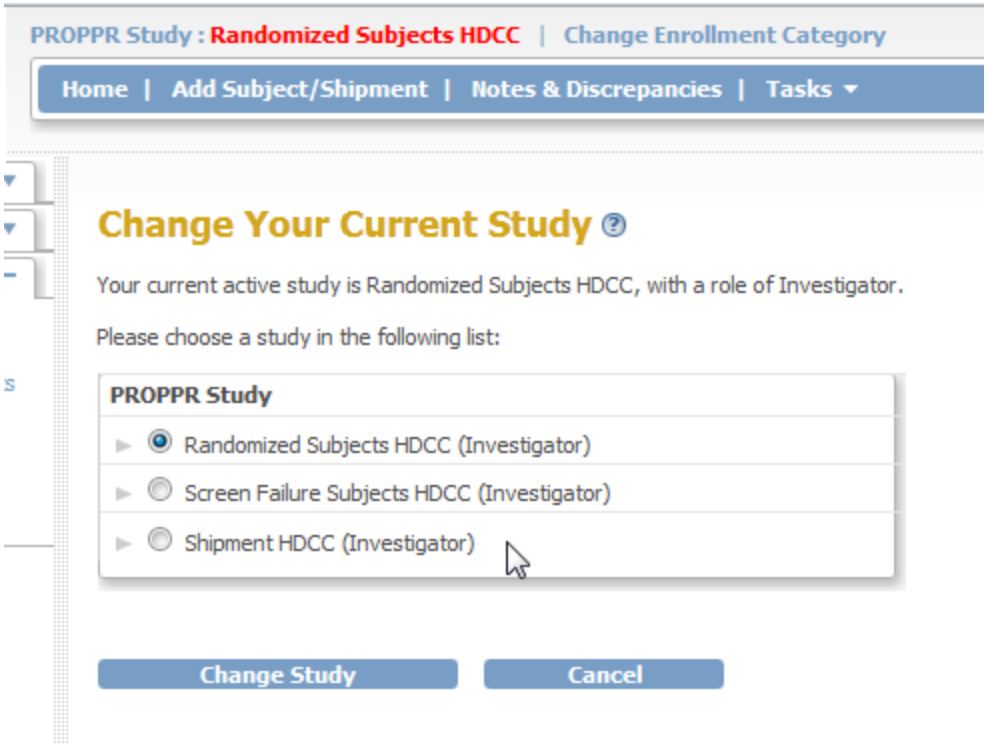
SUBJECT MATRIX

Subject Matrix Overview



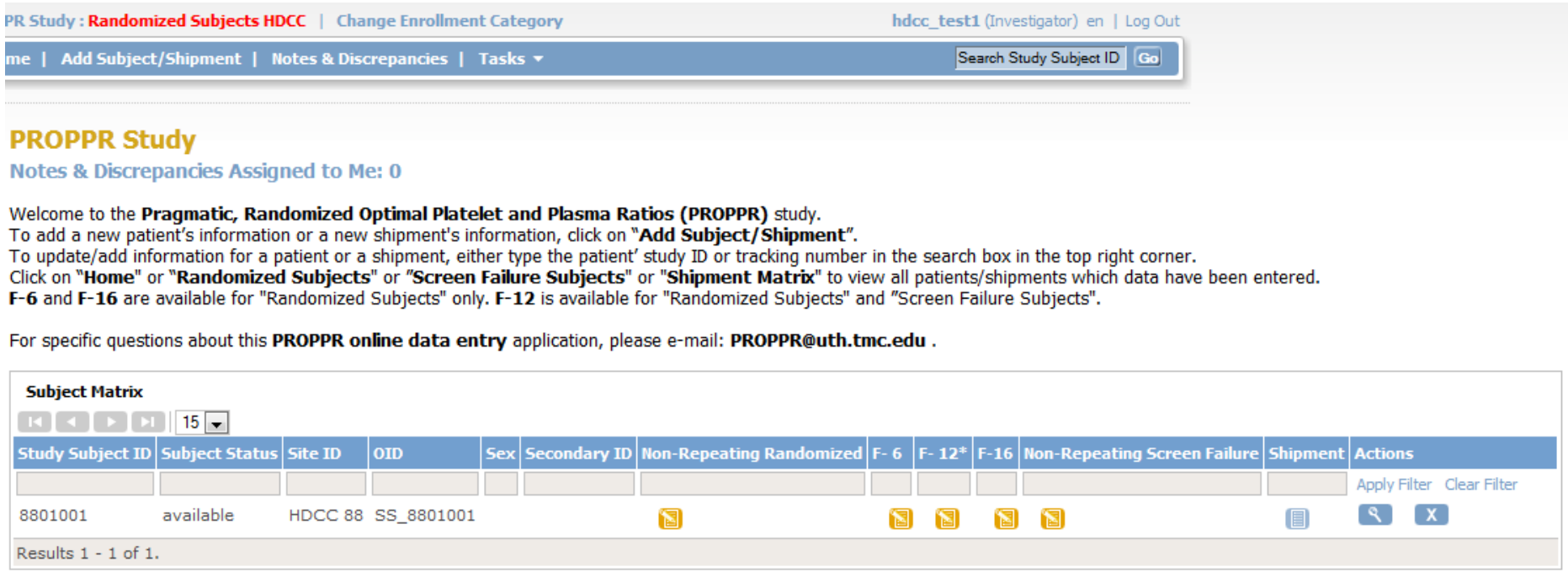
- The Subject Matrix is a table with information for all Subjects in a Study.
- You can view, enter, and update information for Subjects in the Study.
- The Subjects that are displayed depend on the current enrollment category in **red**.
- There is one Subject per row, with the Study Subject ID in the first column.
- Each cell contains an icon that identifies the status of a category for the Subject
- Below the Subject Matrix is a listing of all the PROPPR Case Report Forms (CRF's)

Subject Matrix Overview



- There are three enrollment categories - current enrollment category is designated in **red** at the top of the page.
  - Randomized Subjects
  - Screen Failure Subjects
  - Shipment – for shipping log
- By selecting a category, your home screen will display a Subject Matrix for only those Study Ids that are randomized or screen failures or it will display shipment IDs.

Subject Matrix Overview



- The eCRFs you are given access to depends on the category you select
- Though all three categories are listed in the Subject Matrix, the current enrollment category governs which eCRFs you have access to.

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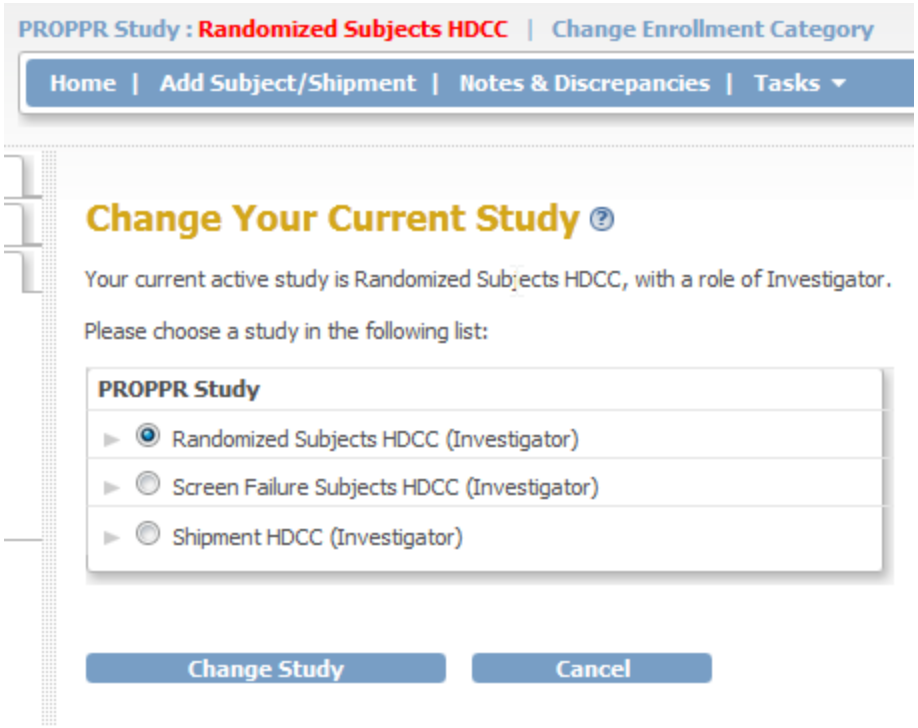
PROPPR Online Database

CHANGE ENROLLMENT CATEGORY EXAMPLES

Change Enrollment Category



- There are three enrollment categories - current enrollment category is designated in **red** at the top of the page.
  - Randomized Subjects
  - Screen Failure Subjects
  - Shipment – for shipping log
- By selecting a category, your home screen will display a Subject Matrix for only those Study IDs that are randomized, screen failures, or ready for shipment

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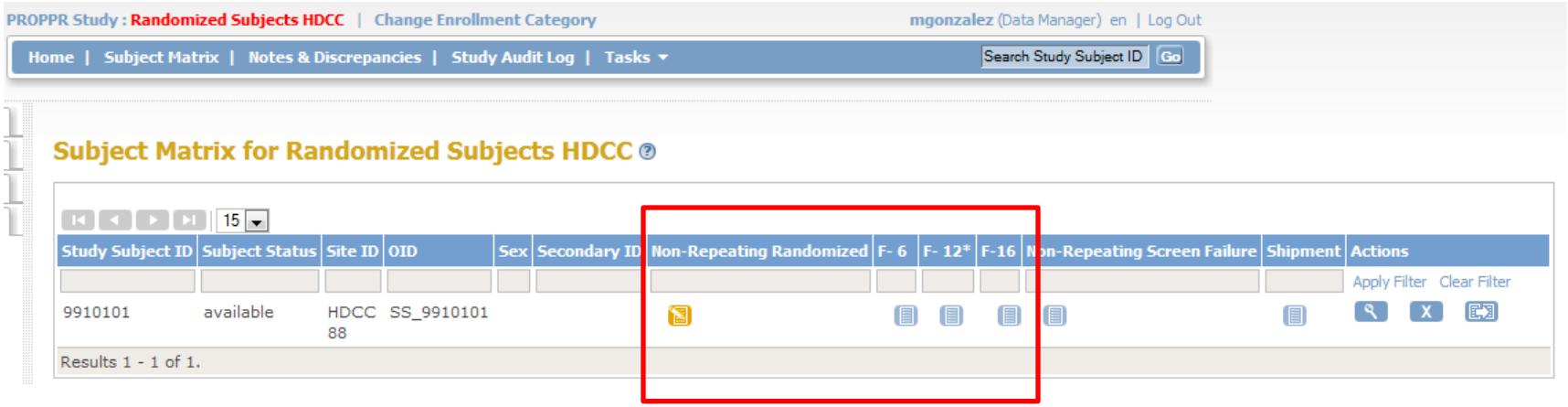
PROPPR Online Database

RANDOMIZED SUBJECT CATEGORY

Change Enrollment Category – Example Randomized Subjects



- There are 23 eCRFs available for a Randomized Subject.
- From the Subject Matrix you can view/enter data for the following eCRFs:
- Non-Repeating Randomized (20 eCRFs)
- Randomized Repeating Forms (3 eCRFs)
    - **F-6** – IV Fluids & Blood Products
    - **F-12*** - Initial 24hrs. Clinical Lab Results
    - **F-16** – 24hr to 30 Day Follow-Up Assessments.
  - These eCRFs are repeating forms so that the PROPPR Online Database upload time can remain manageable.

Example Randomized Subjects – available eCRFs

Enter or Validate Data for Non-Repeating Randomized

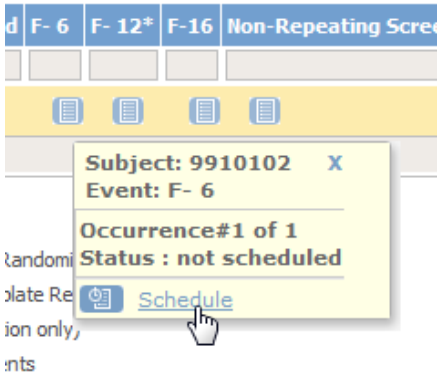
CRFs in this Study Event:

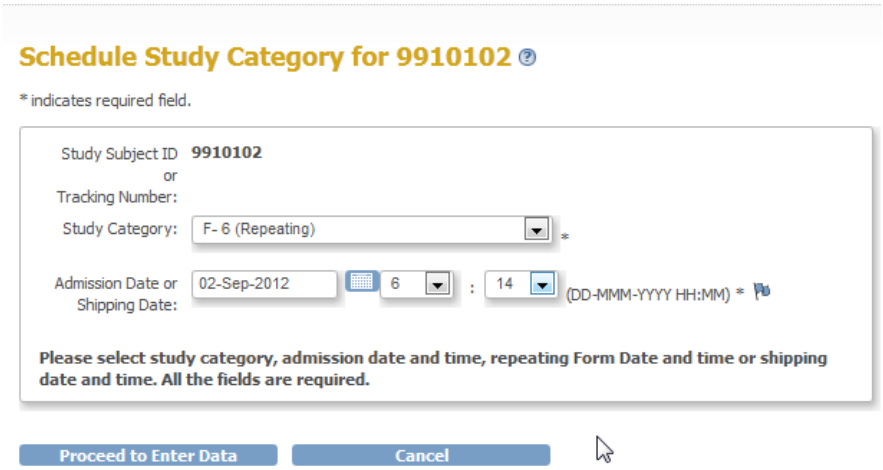
Case Report Form Name	Version	Status	Initial Data Entry	Study Subject ID : 9910101
F- 2	v1.0			Enter Data | View data | Print |
F- 3	v1.0			Enter Data | View data | Print |
F- 4	v1.0			Enter Data | View data | Print |
F- 5	v1.0			Enter Data | View data | Print |
F- 7	v1.0			Enter Data | View data | Print |
F- 8	v1.0			Enter Data | View data | Print |
F- 9	v1.0			Enter Data | View data | Print |
F-10	v1.0			Enter Data | View data | Print |
F-11	v1.0			Enter Data | View data | Print |
F-13	v1.0			Enter Data | View data | Print |
F-14	v1.0			Enter Data | View data | Print |
F-15	v1.0			Enter Data | View data | Print |
F-21	v1.0			Enter Data | View data | Print |
F-17	v1.0			Enter Data | View data | Print |
F-22	v1.0			Enter Data | View data | Print |
F-18	v1.0			Enter Data | View data | Print |
F-19	v1.0			Enter Data | View data | Print |
F-23	v1.0			Enter Data | View data | Print |
F-20	v1.0			Enter Data | View data | Print |
F- 1	v1.0			Continue Enter | View data | Print | Remove | Delete

View this Subject's Record | Exit

- **Example:** Within the **Randomized Subjects** category, if you select View/Enter Data for the **Non-Repeating Randomized** eCRFs, you will be given access to a list of eCRFs that are available for you to enter data for a Randomized Subject.
- These are the 20 non-repeating forms
- The admission date is pre-populated for these forms. You can begin entering data in these forms by clicking once on Enter Data.

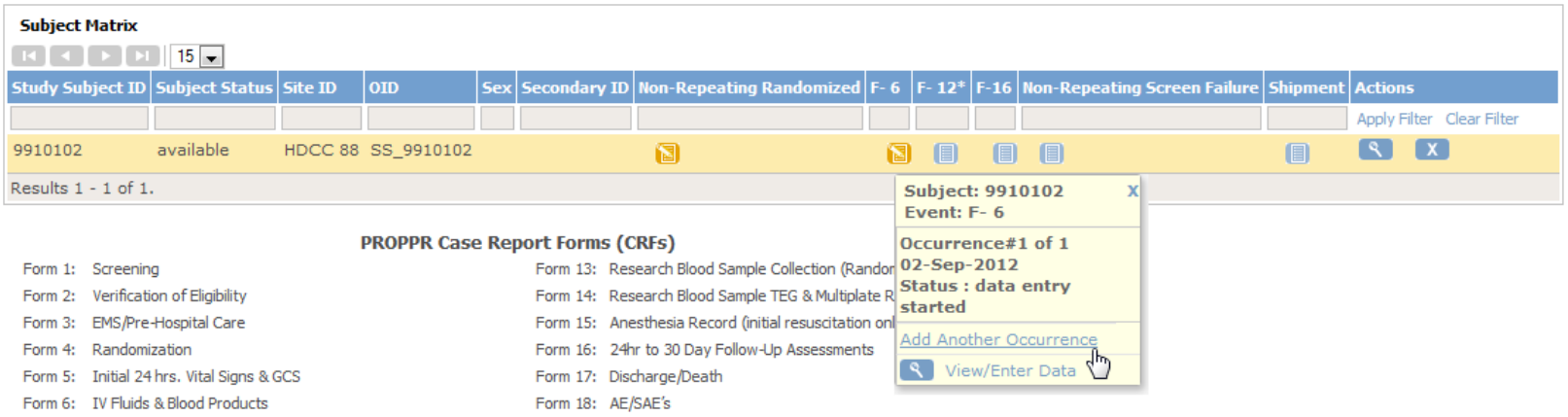
Example Randomized Subjects – available eCRFs F-6



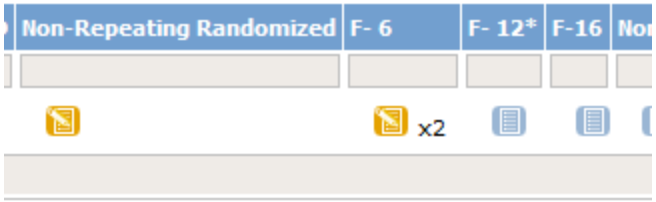


- Within the **Randomized Subjects** category, if you select View/Enter Data for the **F-6** eCRF, you will be asked to enter the Repeating Form Date and Time of the IV Fluid or Blood Product, and then allowed to begin entering data for this eCRF.
- The repeating form date and time:
  - This is the IV Fluid/Blood product transfusion date and time recorded on CRF 6.
- **This is a repeating form, there will be one form per product.**

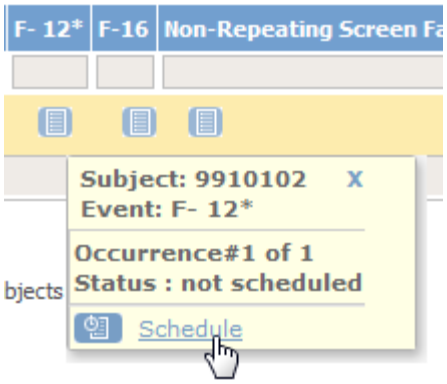
Example Randomized Subjects – available eCRFs F-6



- eCRF F-6 will need to be completed for each IV Fluid or Blood Product.
- To begin entering data for more than one IV Fluid or Blood Product:
  1. Click Once on Add Another Occurrence
  2. Enter the IV Fluid/Blood Product Transfuison date and time
  3. Click Once on Proceed to Enter Data
  4. Click Once on Enter Data, begin entering data for F-6
- For every fluid/product entered, a counter to the right of the F-6 icon will show
- Repeat these steps for each Fluid/Product

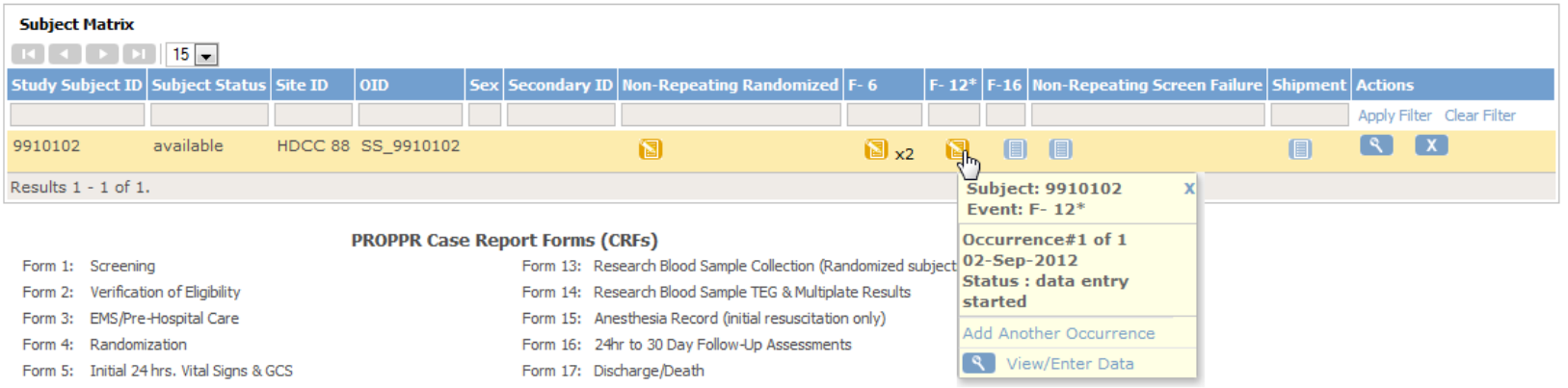


Example Randomized Subjects – available eCRFs F-12

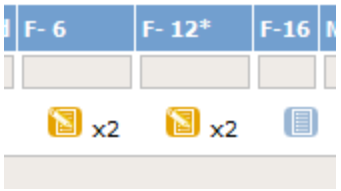


- Within the **Randomized Subjects** category, if you select View/Enter Data for the **F-12** eCRF, you will be asked to enter the Repeating Form Date and Time of the Clinical Lab Tests, and then allowed to begin entering data for this eCRF.
- This is a repeating form, there will be one form per date and time recorded on the CRF F-12.

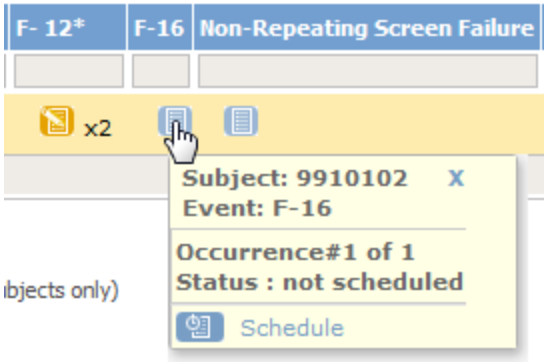
Example Randomized Subjects – available eCRFs F-12



- eCRF F-12 will need to be completed for each date and time recorded on CRF F-12.
- To begin entering data for more than one Clinical Lab results:
  1. Click Once on Add Another Occurrence
  2. Enter the date and time
  3. Click Once on Proceed to Enter Data
  4. Click Once on Enter Data, begin entering data for F-12
- For every date and time entered, a counter to the right of the F-12 icon will show
- Repeat these steps for each date and time

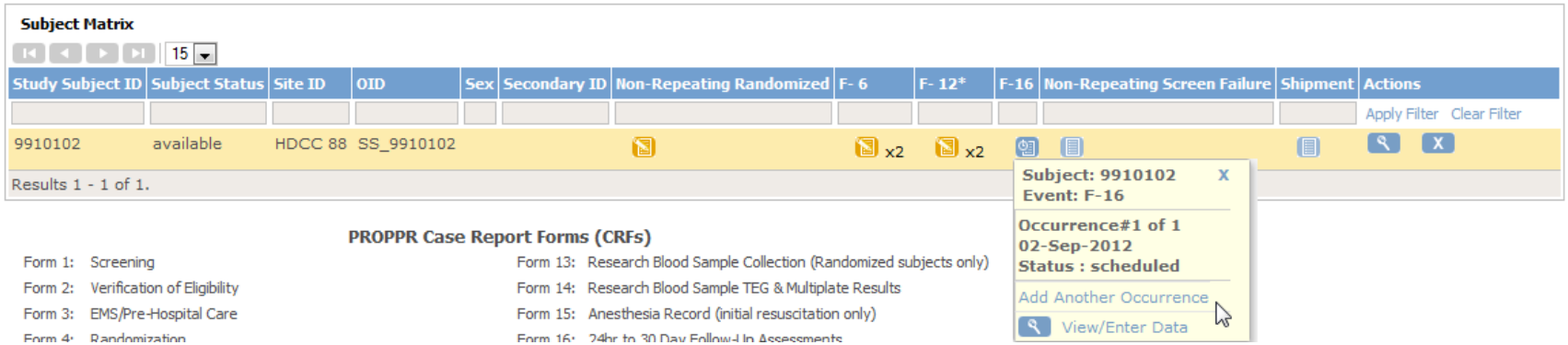


Example Randomized Subjects – available eCRFs F-16

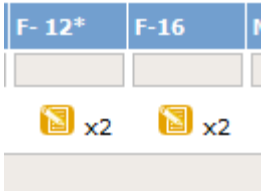


- Within the **Randomized Subjects** category, if you select View/Enter Data for the **F-16** eCRF, you will be asked to enter the Repeating Form Date and Time of the Follow-Up Assessment, and then allowed to begin entering data for this eCRF.
- Repeating form date and time:
  - This is the date and time of the Follow Up Assessment recorded on CRF 16
- This is a repeating form, there will be one form per date and time of each Follow-Up Assessment.

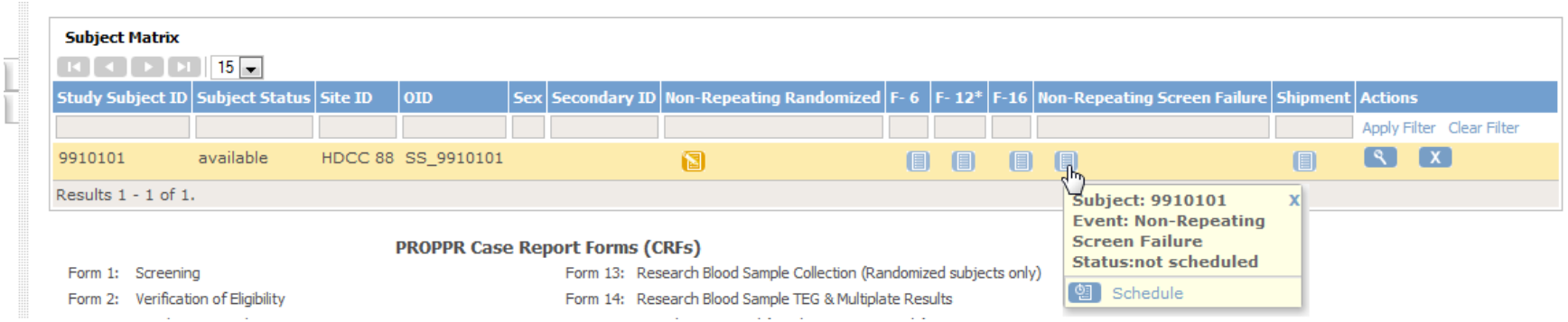
Example Randomized Subjects – available eCRFs F-16



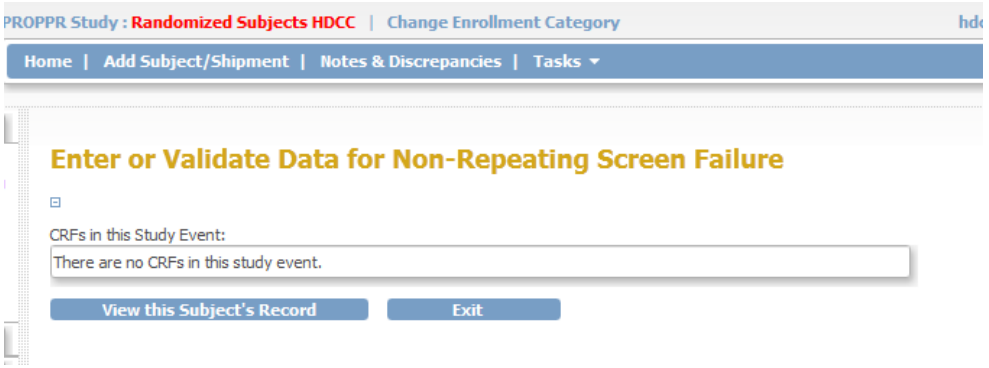
- eCRF F-16 will need to be completed for the date and time of each Follow-Up Assessment.
- To begin entering data for more than one Follow-Up Assessment:
  1. Click Once on Add Another Occurrence
  2. Enter the date and time
  3. Click Once on Proceed to Enter Data
  4. Click Once on Enter Data, begin entering data for F-16
- For every Follow-Up Assessment entered, a counter to the right of the F-16 icon will show
- Repeat these steps for each Follow-Up Assessment



Example Randomized Subjects – Non-available eCRFs



- Within the **Randomized Subjects** category, if you select Schedule for the **Non-Repeating Screen Failure** or **Shipment** eCRFs, after entering the date and time, you will see the screen to the right. This screen states that there are no eCRFs available.
- Even though the eCRF category is listed in the Subject Matrix, your **current category** (at top in red), governs which eCRFs you have access to.



PROPPR

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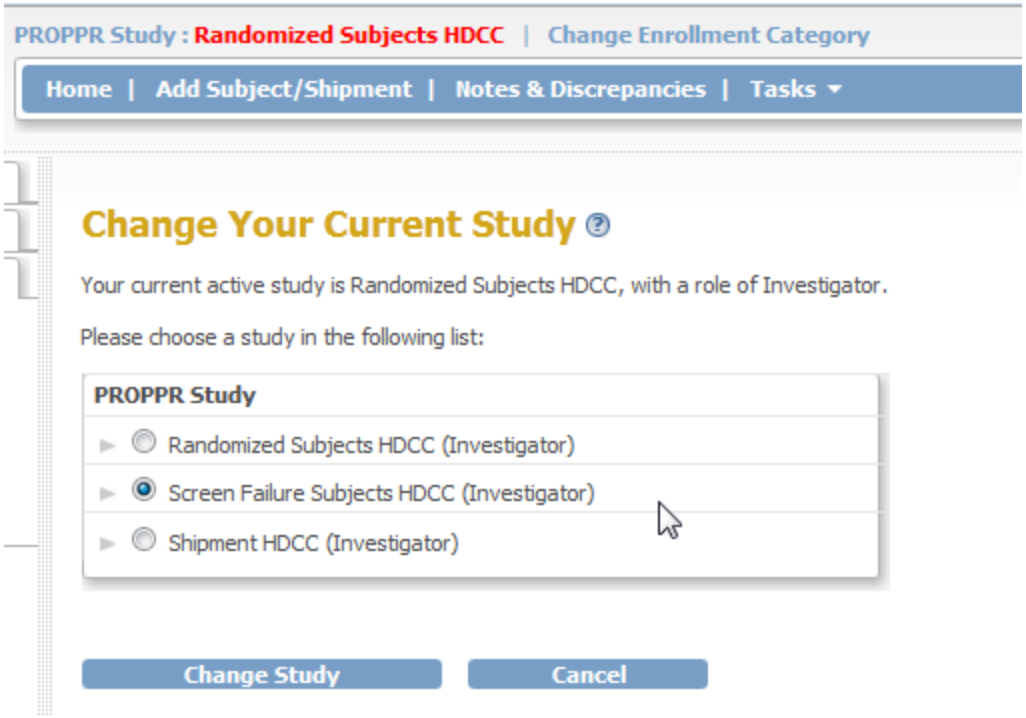
PROPPR Online Database

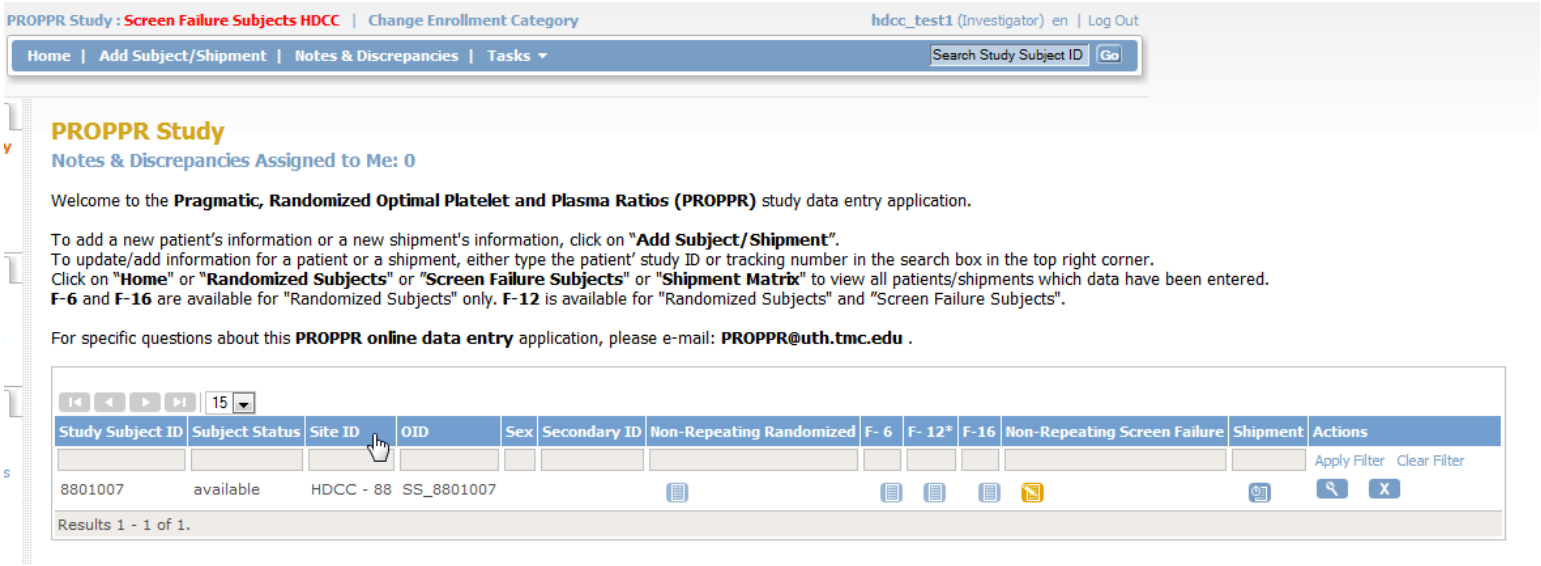
SCREEN FAILED SUBJECT CATEGORY

Change Enrollment Category – Screen Failure Subjects



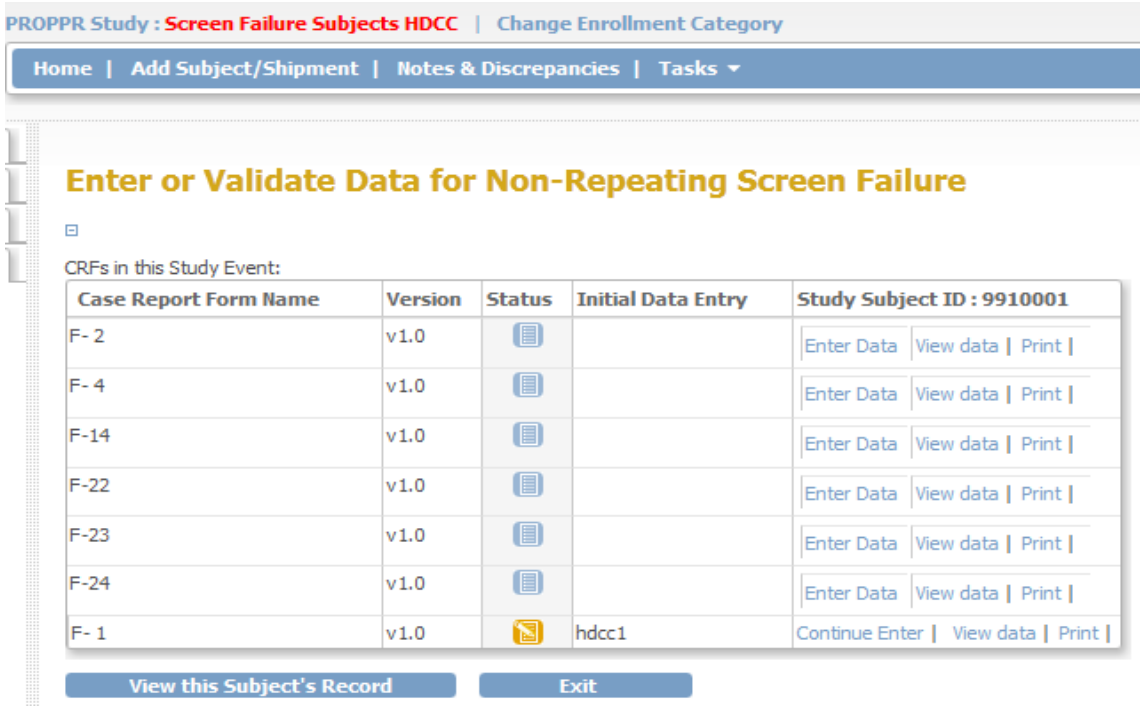
- Three enrollment categories – current category in **red**
  - Randomized Subjects
  - Screen Failure Subjects
  - Shipment
- By selecting a category, your home screen will display a Subject Matrix for only those Study IDs that are randomized, screen failures, or ready for shipment
- Choose **Screen Failure Subjects** to change categories

Change Enrollment Category – Example Screen Failure Subjects



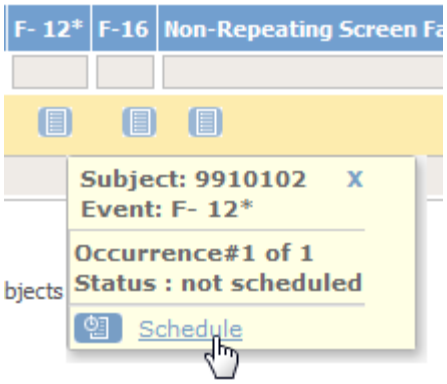
- There are 8 eCRFs available for a Screen Failure Subject.
- From the Subject Matrix you can view/enter data for the following eCRFs:
- Non-Repeating Screen Failure (7 eCRFs)
- Screen Failure Repeating Forms (1 eCRFs)
    - **F-12*** - Initial 24hrs. Clinical Lab Results
    - This eCRF is a repeating form so that the PROPPR Online Database upload time can remain manageable.

Example Screen Failure Subjects – available eCRFs



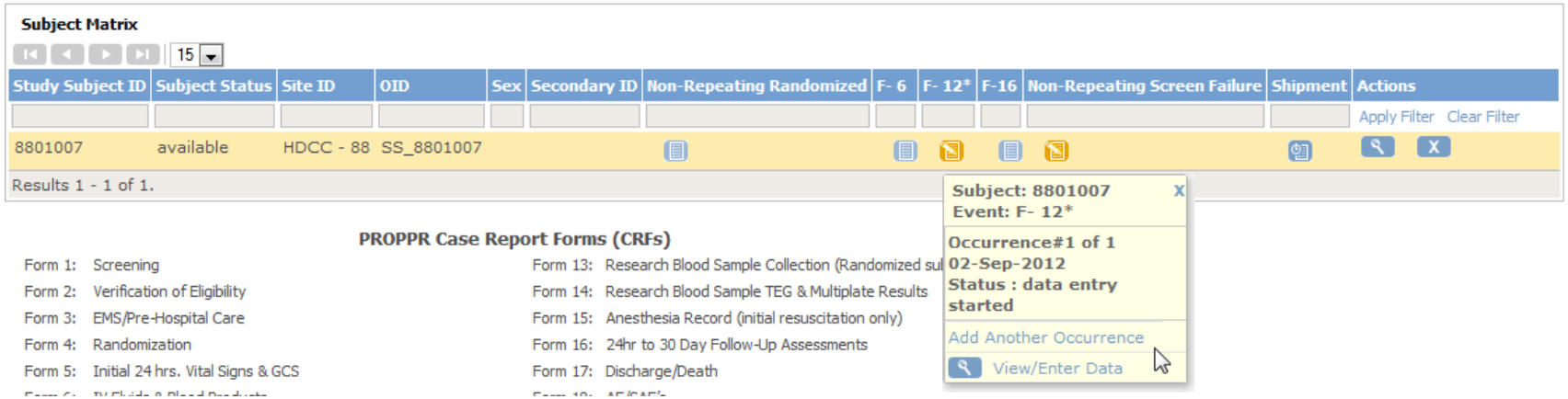
- **Example:** Within the **Screen Failure Subjects** category, if you select View/Enter Data for the Non-Repeating Screen Failure eCRFs, you will see this screen. This is the list of the Non-Repeating eCRFs for a Screen Failure subject.

Example Screen Failure Subjects – available eCRFs F-12

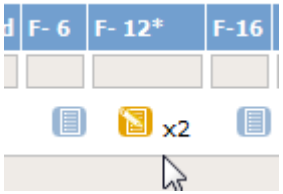


- Within the **Screen Failure Subjects** category, if you select View/Enter Data for the **F-12** eCRF, you will be asked to enter the Repeating Form Date and Time of the Clinical Lab Tests, and then allowed to begin entering data for this eCRF.
- Repeating Form Date and Time:
  - This is the Date and Time of each set of Clinical Lab Results recorded on CRF 12
- This is a repeating form, there will be one form per date and time recorded on the CRF F-12.

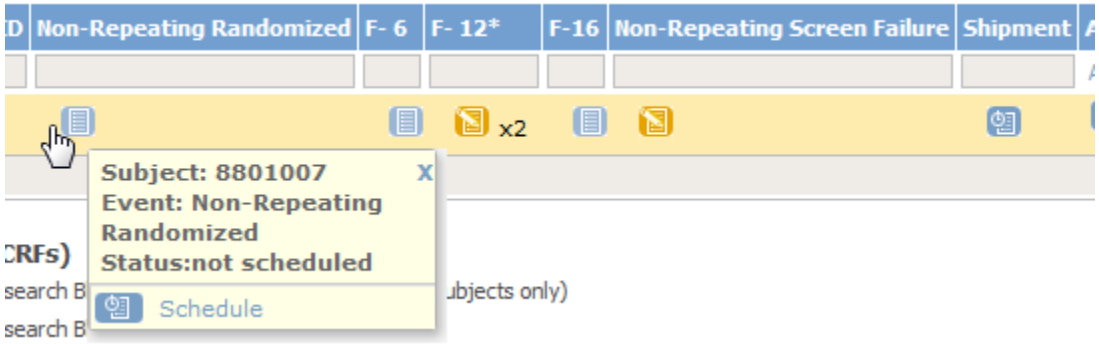
Example Screen Failure Subjects – available eCRFs F-12



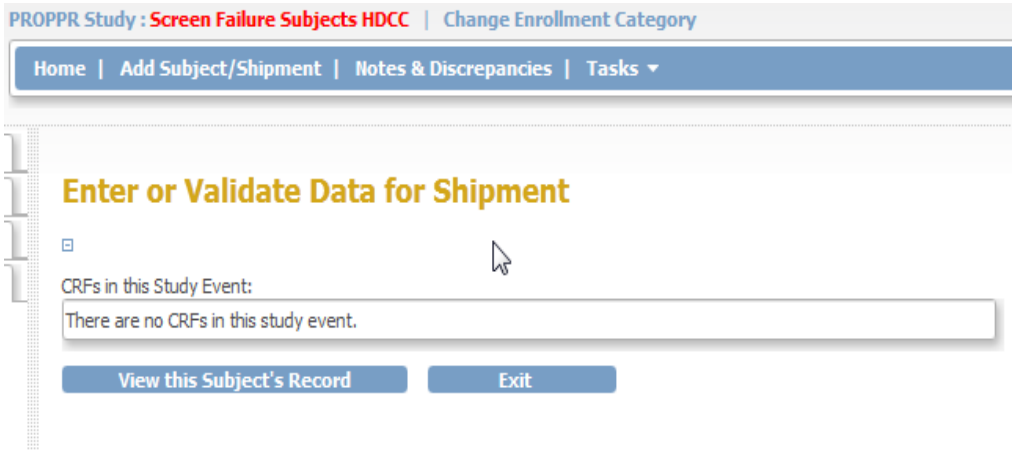
- eCRF F-12 will need to be completed for each date and time recorded on CRF F-12.
- To begin entering data for more than one Clinical Lab results:
  1. Click Once on Add Another Occurrence
  2. Enter the date and time
  3. Click Once on Proceed to Enter Data
  4. Click Once on Enter Data, begin entering data for F-12
- For every date and time entered, a counter to the right of the F-12 icon will show
- Repeat these steps for each date and time



Change Enrollment Category – Example Screen Failure Subjects



- Within the **Screen Failure Subjects** category, if you select Schedule for the following
  - Non-Repeating Randomized eCRFs
  - F-6 eCRF
  - F-16 eCRF
  - Shipment eCRF (Shipping Log)
- You will see the screen to the right. This screen states that there are no eCRFs available.
- Even though the eCRF is listed in the Subject Matrix, your current category (at top in red), governs which eCRFs you have access to.



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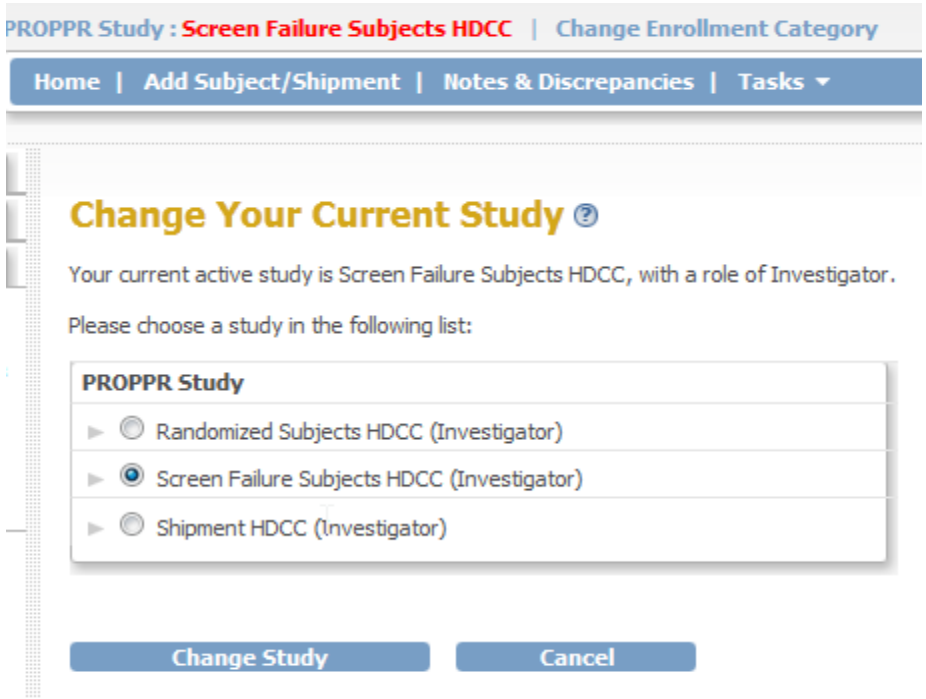
PROPPR Online Database

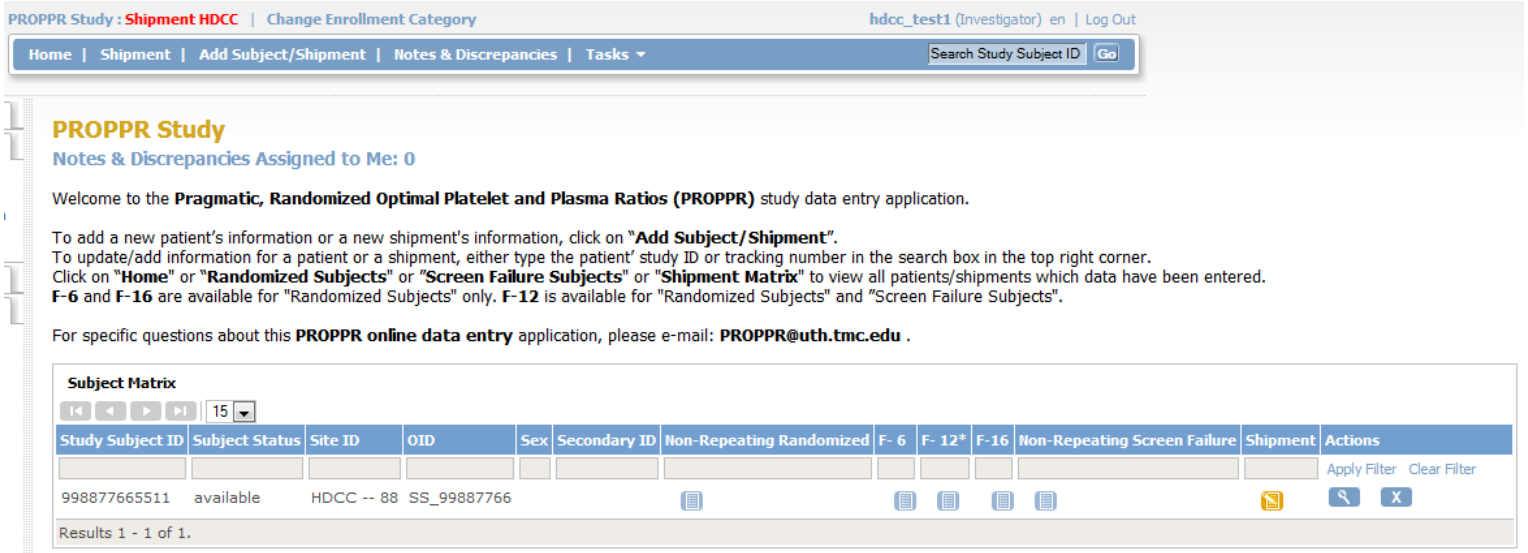
SHIPMENT CATEGORY

Change Enrollment Category - Shipment

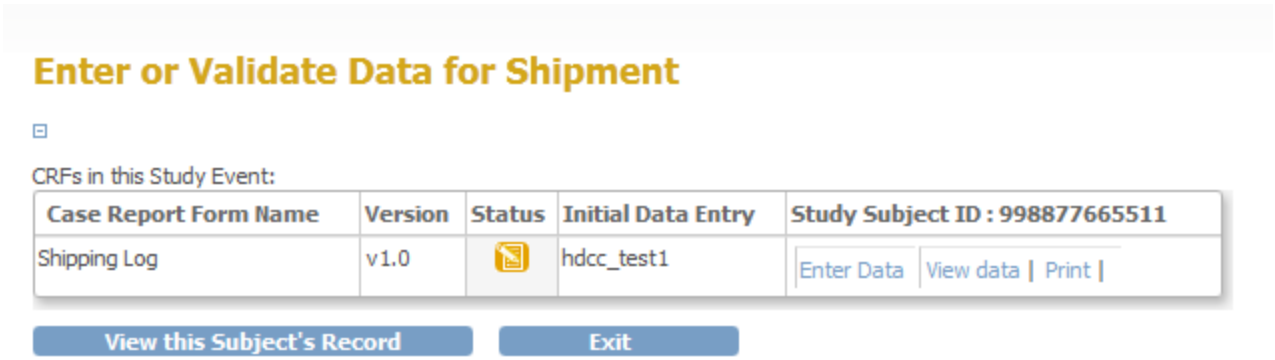


- Three enrollment categories – current category in **red**
  - Randomized Subjects
  - Screen Failure Subjects
  - Shipment
- By selecting a category, your home screen will display a Subject Matrix for only those Study IDs that are randomized, screen failures, or ready for shipment
- Choose **Shipment** to change categories

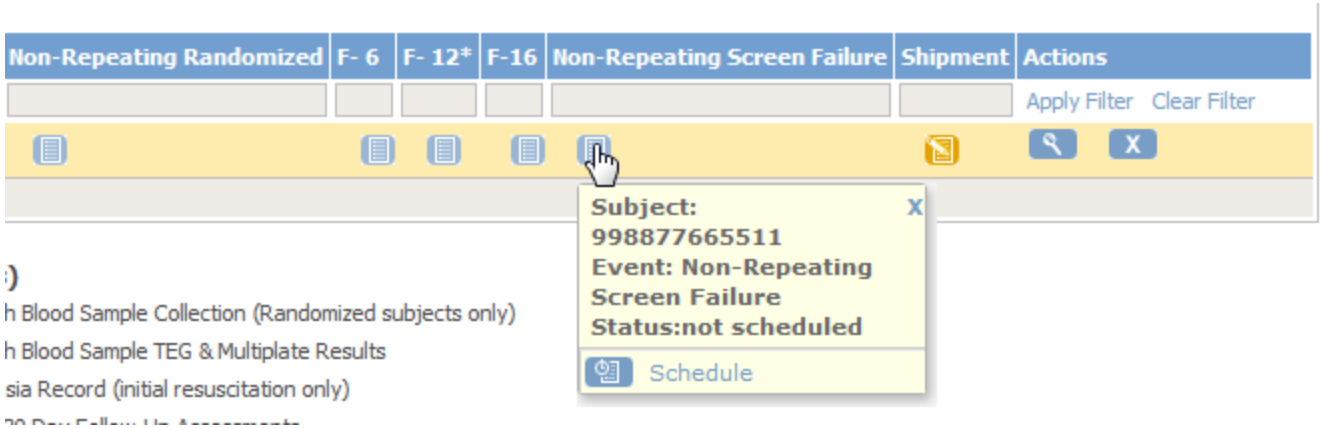
Change Enrollment Category – Example Screen Failure Subjects



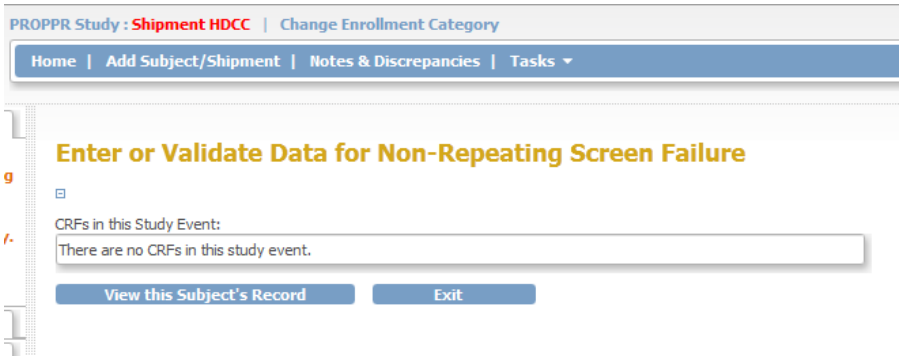
- The Shipping Log is the only eCRF available for a Shipment.



Change Enrollment Category – Example Screen Failure Subjects



- Within the **Screen Failure Subjects** category, if you select Schedule for the following
  - Non-Repeating Randomized eCRFs
  - F-6 eCRF
  - F-16 eCRF
  - Non-Repeating Screen Failure eCRFs
- You will see the screen to the right. This screen states that there are no eCRFs available.
- Even though the eCRF is listed in the Subject Matrix, your current category (at top in red), governs which eCRFs you have access to.



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SUBJECT/SHIPMENT IDS

Subject ID format & range for each site

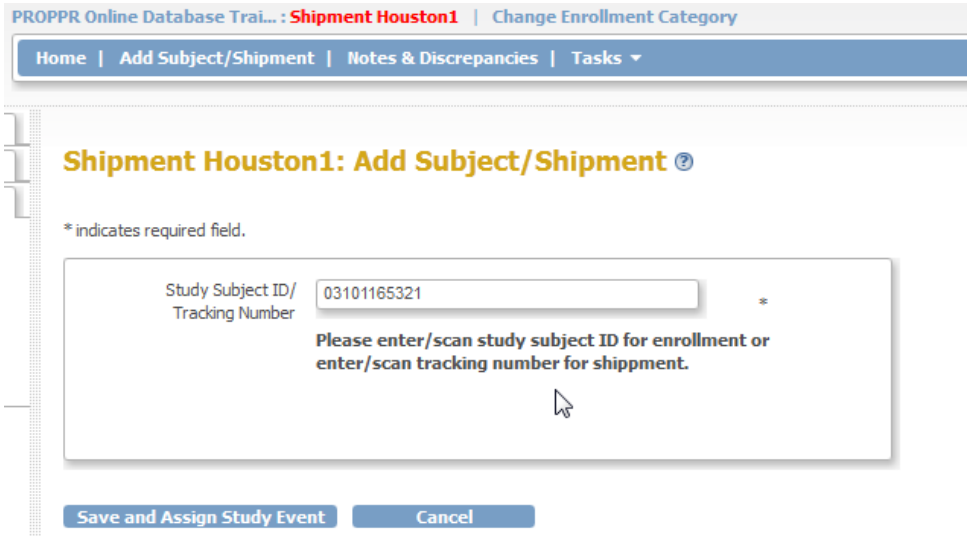
Site ID	Site Name	Subject ID Range
10	UT Houston	1010001 – 1019999
12	UC-SF	1210001 – 1219999
14	Cincinnati	1410001 – 1419999
16	Sunnybrook	1610001 – 1619999
18	Baltimore	1810001 – 1819999
20	Milwaukee	2010001 – 2019999
22	Portland	2210001 – 2219999
24	Birmingham	2410001 – 2419999
26	Tucson	2610001 – 2619999
28	USC	2810001 – 2819999
30	Memphis	3010001 – 3019999
32	Seattle	3210001 – 3219999

- The Subject ID for PROPPR is 7 digits long:
- The first 2 digits represent the Site using the ID from the table.
- The remaining five digits represent the Subject.
- The Subject IDs are going to be in sequential order.
- The range of the Subject IDs is:
  - **XX10001 – XX19999**

  where XX(the first 2 digits) represent the Site ID
  - So, for your site, the first two digits will always be your Site ID

Shipment ID

- The Shipment ID will be represented by the shipping carrier's tracking number:
- The Shipment ID for PROPPR cannot not be longer than 30 characters
- **Example:** FedEx uses a 12 digit tracking number, enter this number for the Shipping ID.



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ADD SUBJECT

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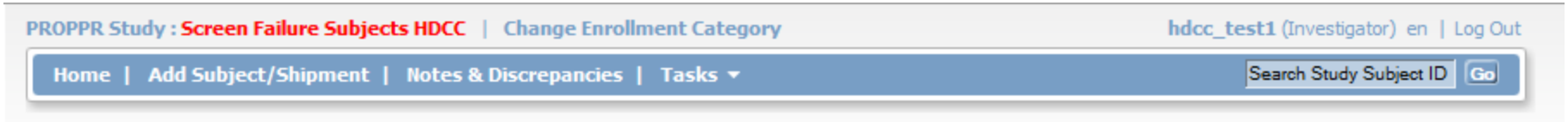
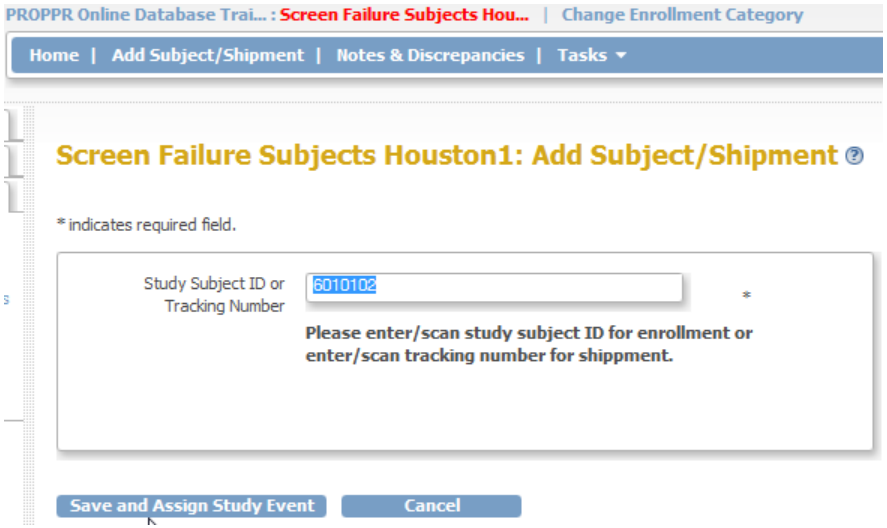
ADD SUBJECT – SCREENING FAILURE

Add a Subject – Enroll a subject – Screen Failure Category

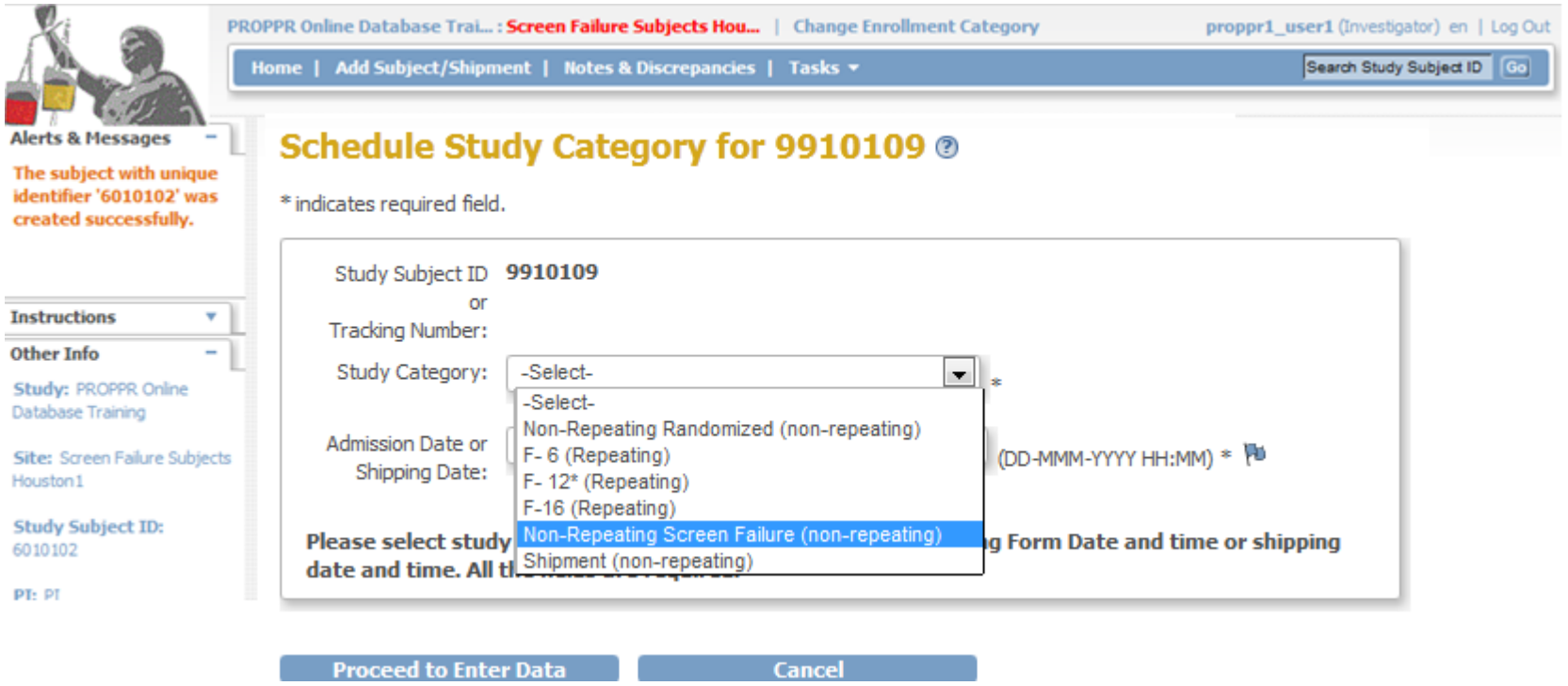


- Click once on the Add Subject/Shipment link.
- The Add New Subject/Shipment Page appears



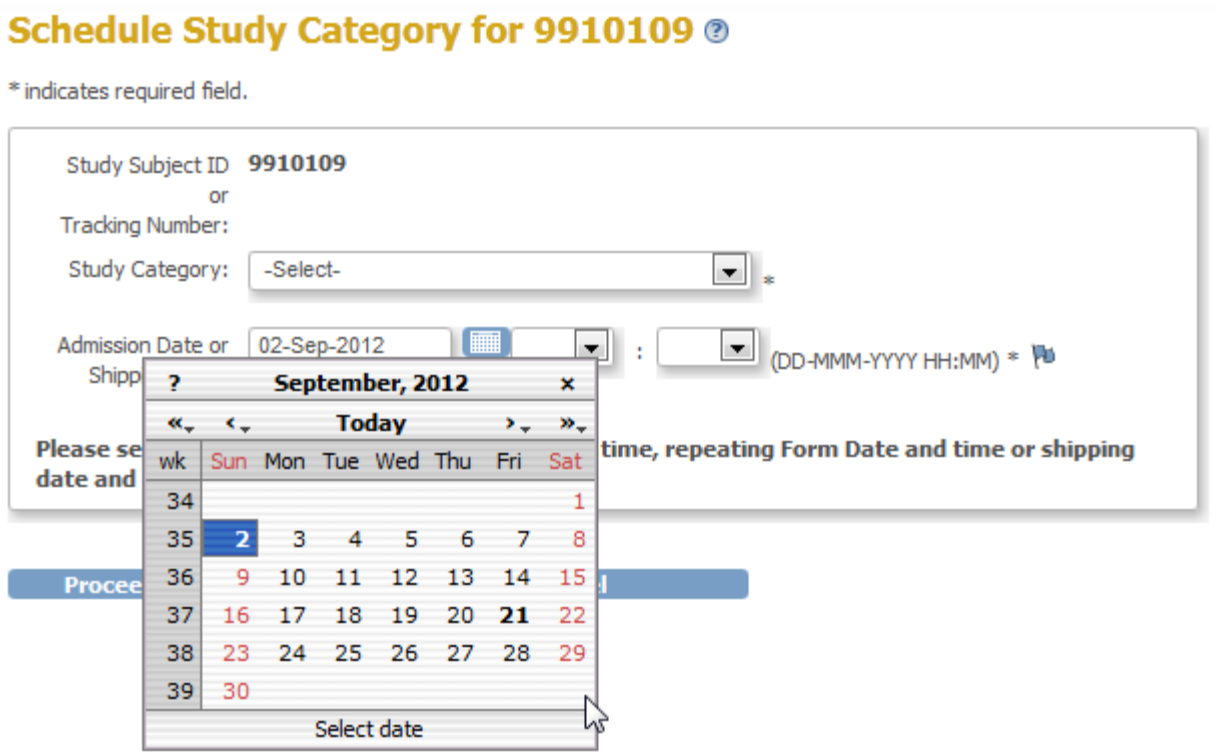
- Before entering the Study Subject ID, make sure that the current enrollment category in **red**, is correct. If it is correct, enter the Study ID and click once on Save and Assign Study Event to add the new Subject ID to your site.
- If the category is not correct, click cancel and then change the current enrollment category to the correct one.
- **If you assign a Study ID to the wrong enrollment category, you will not have access to the correct eCRFs and will not be able to change the enrollment category for that Subject without contacting the HDCC**

Add a Subject Screen Failure Subject



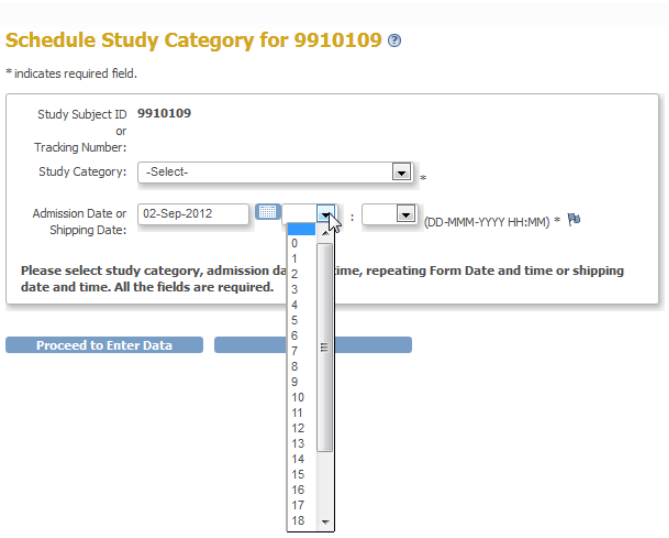
- Once the Study Subject ID is saved, you can continue enrolling a Subject in the correct enrollment category by selecting the category from the drop down list
- Selecting the correct category is important, as explained in the examples earlier, you will only have access to the eCRFs for a Subject, based on the enrollment category selected.
- For a Screen Failure Subject, select **Non – Repeating Screen Failure Subjects** from the drop down list as shown.
- This will make the eCRFs for a Screen Failure Subject available for data entry.

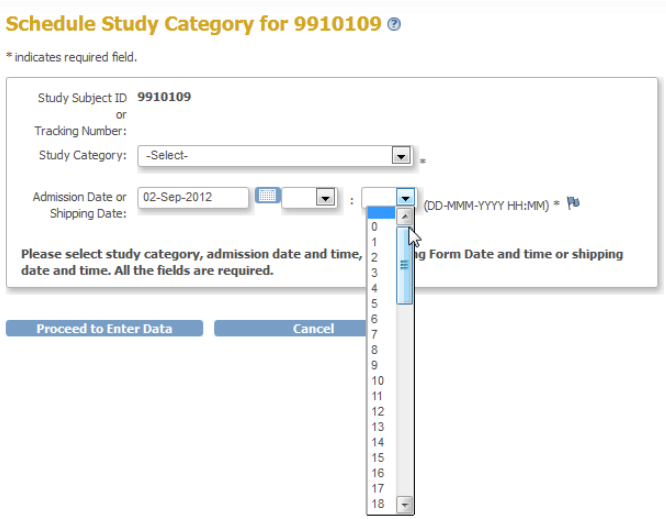
Add a Subject Screen Failure Subject



- Enter the date by clicking once on the calendar icon to the right of the date input box.
  - The date must be in **DD-MMM-YYYY** format

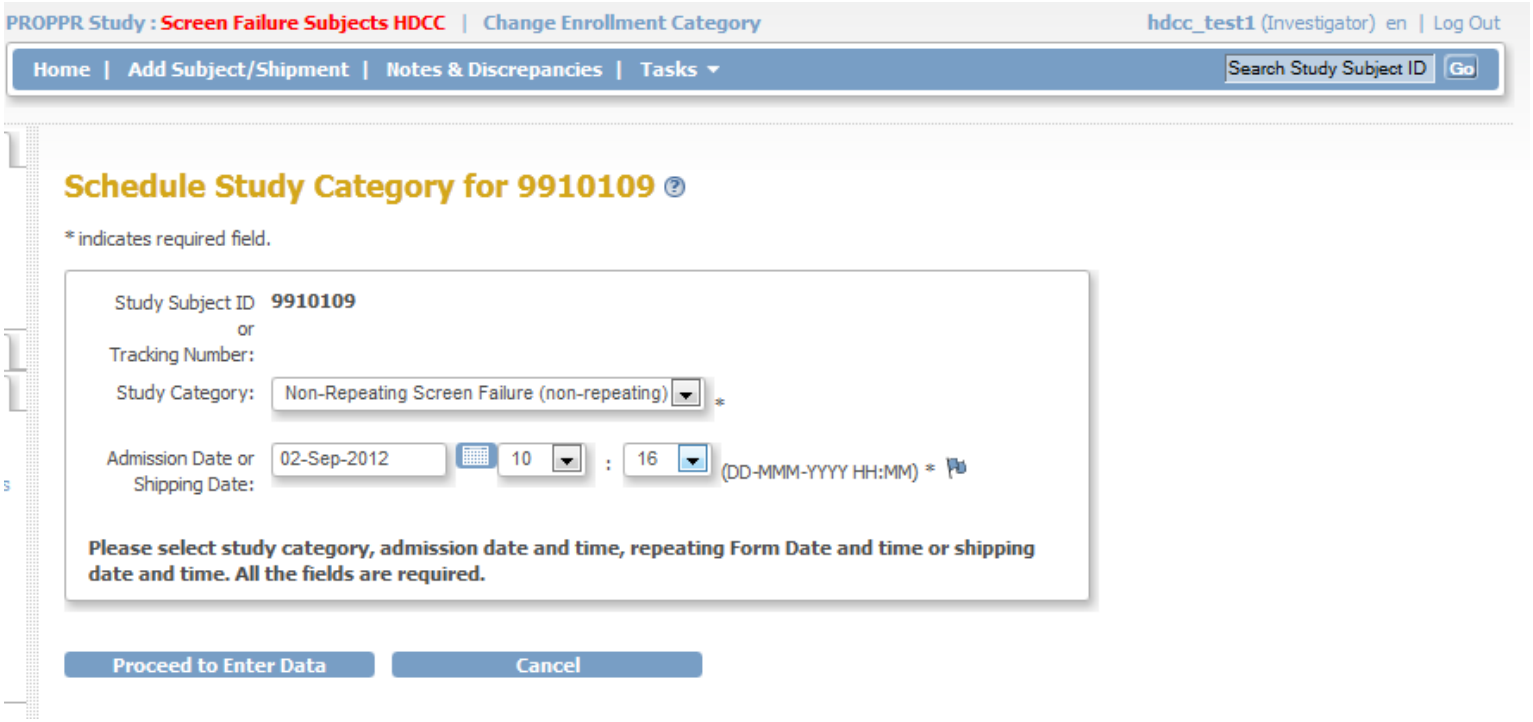
Add a Subject Screen Failure Subject





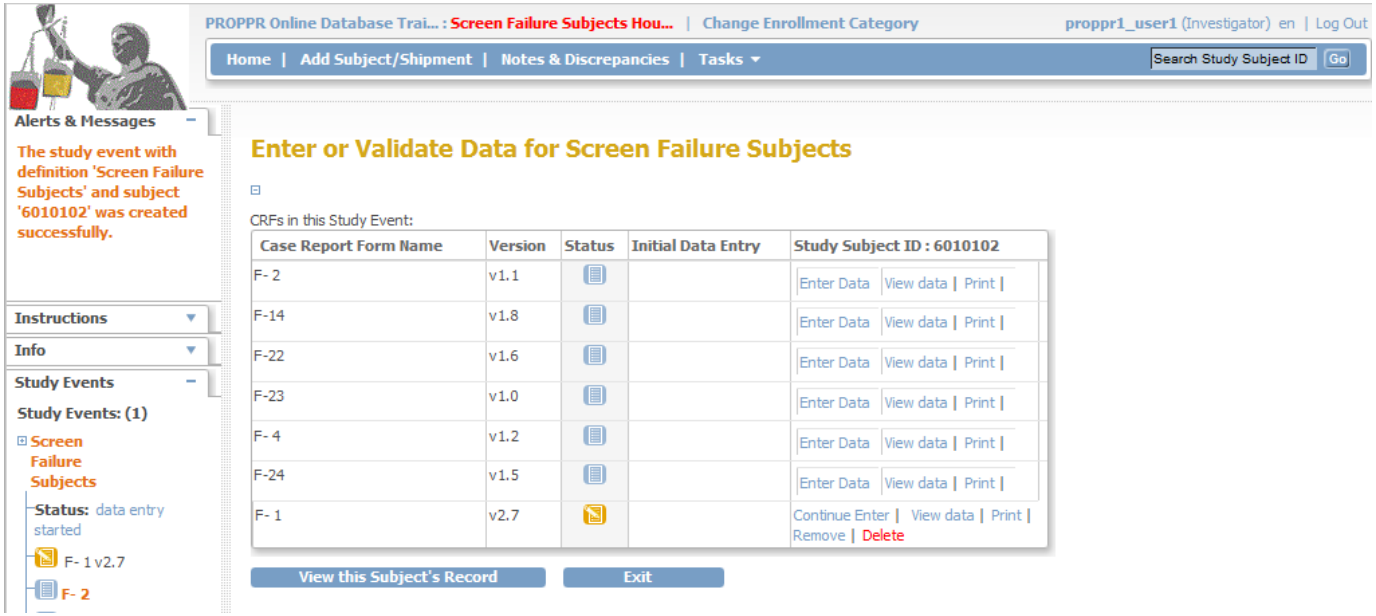
- Enter time from the drop down list provided
  - The time will be in **HH:MM** format

Add a Subject Screen Failure Subject



- Study eCRF – make sure it is for the correct enrollment category in **red**
- Once you have selected the correct enrollment category and have entered the date and time, you can click once on Proceed to Enter Data, to view which eCRFs are available for data entry.

Add a Subject Screen Failure Subject



- **8 eCRFs** - These and only these eCRFs are available for data entry for a Screen Failure Subject:
  - **eCRF 1** – status is data entry started, represented by the orange icon
  - **eCRF 2** – status is ready for data entry
  - **eCRF 4** – status is ready for data entry
  - **eCRF 14** – status is ready for data entry
  - **eCRF 22** - status is ready for data entry
  - **eCRF 23** -status is ready for data entry
  - **eCRF 24** - status is ready for data entry
  - **eCRF 12** – this is a repeating form and is accessible from the Subject Matrix, a date and time must be entered for each set of clinical lab results

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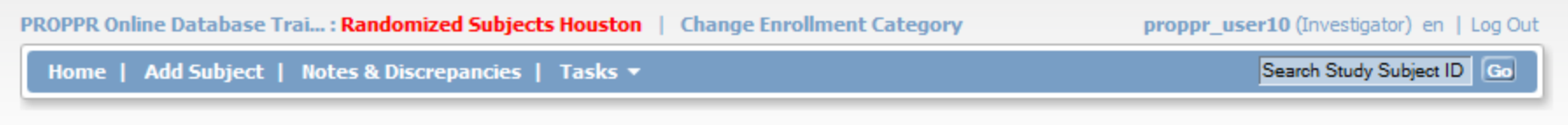
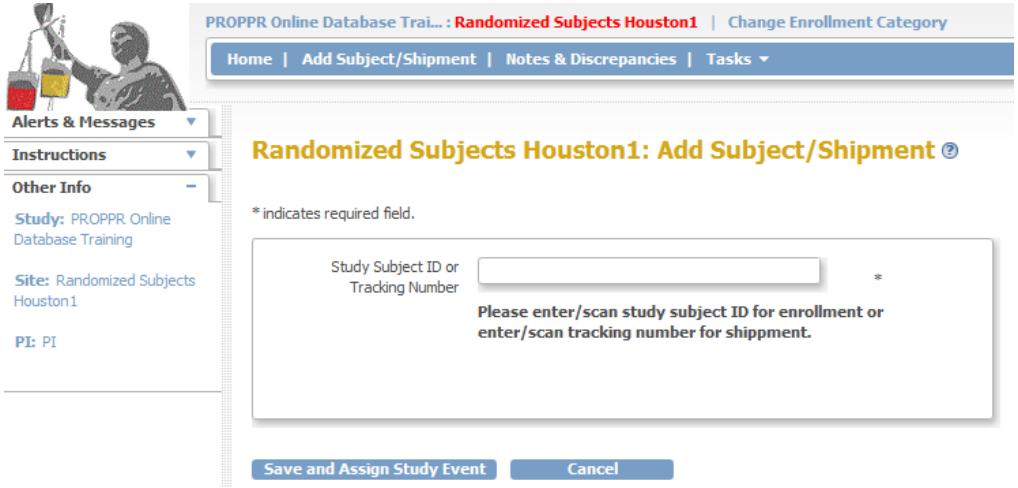
ADD SUBJECT – RANDOMIZED

Add a Subject – Enroll a subject – Randomized Category

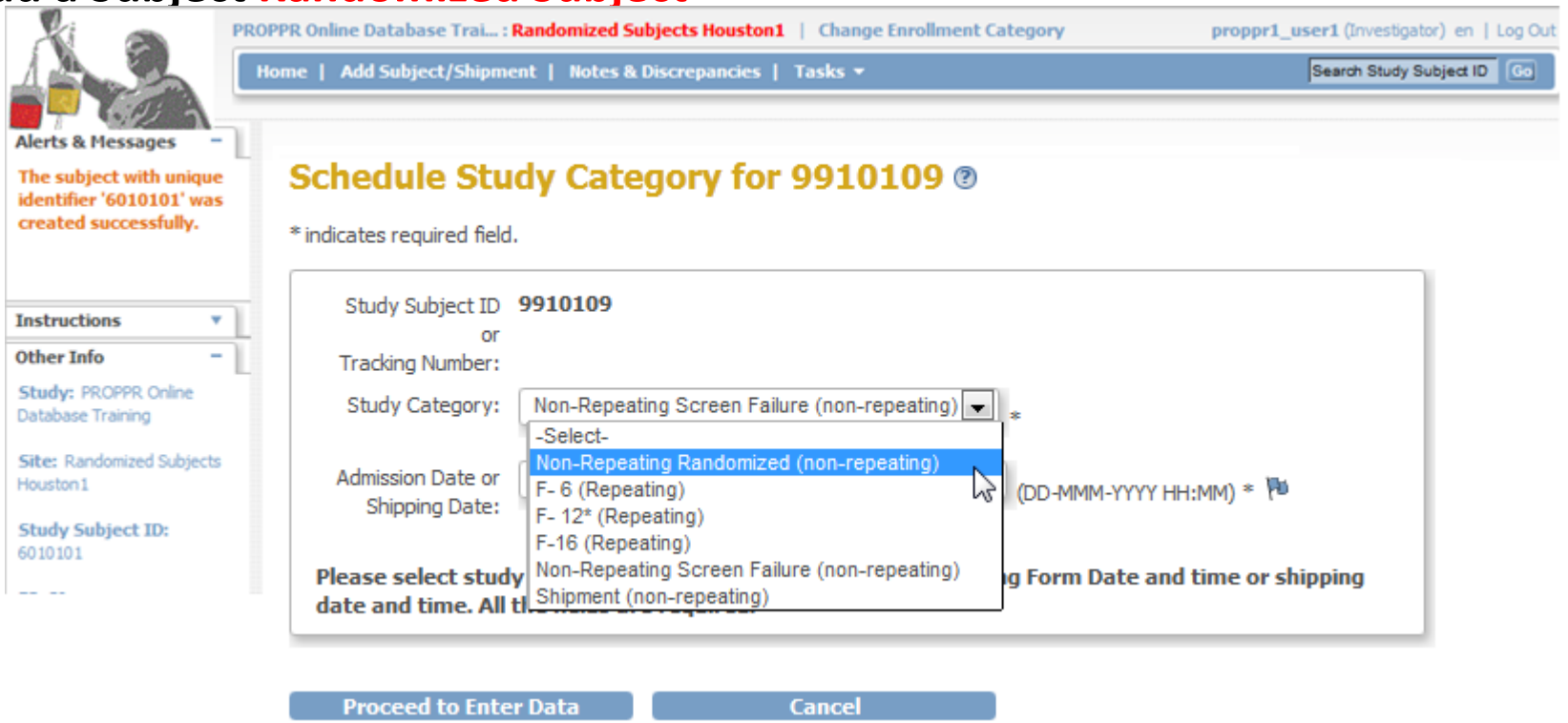


- Click once on the Add Subject link.
- The Add New Subject/Shipment Page appears



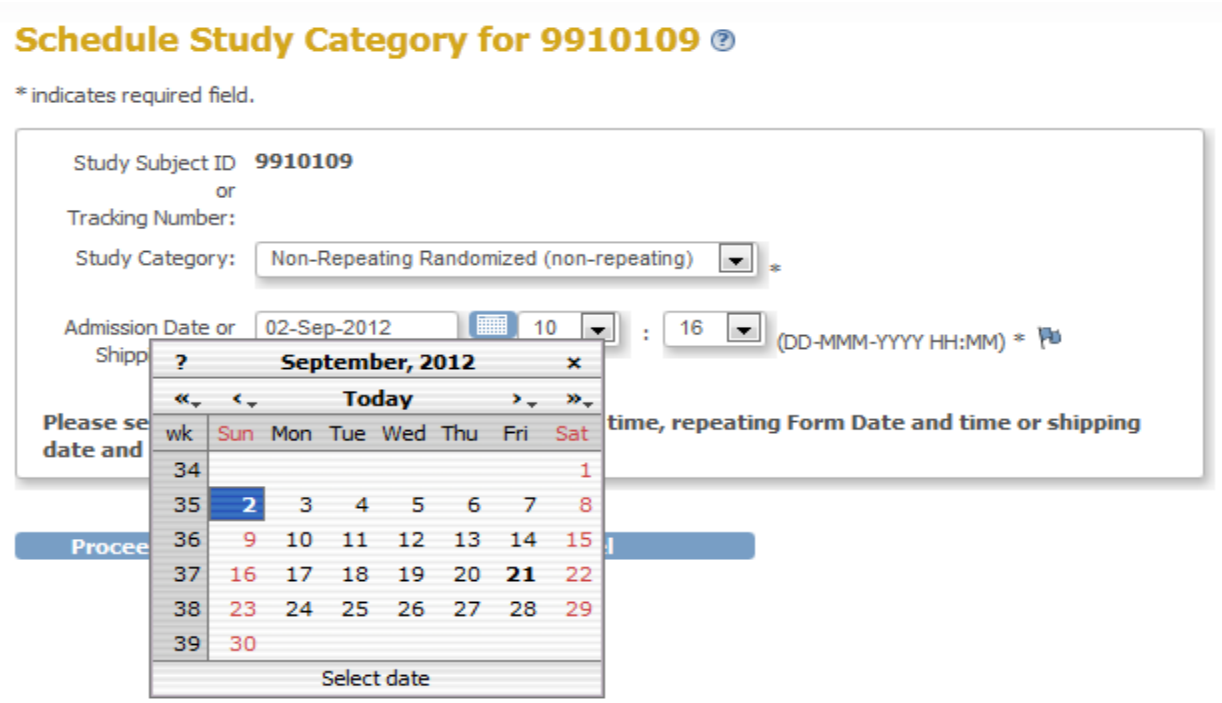
- Before entering the Study Subject ID, make sure that the current enrollment category in **red**, is correct. If it is correct, enter the Study ID and click once on Save and Assign Study Event to add the new Subject ID to your site.
- If the category is not correct, click cancel and then change the current enrollment category to the correct one.
- **If you assign a Study ID to the wrong enrollment category, you will not have access to the correct eCRFs and will not be able to change the enrollment category for that Subject without contacting the HDCC**

Add a Subject Randomized Subject



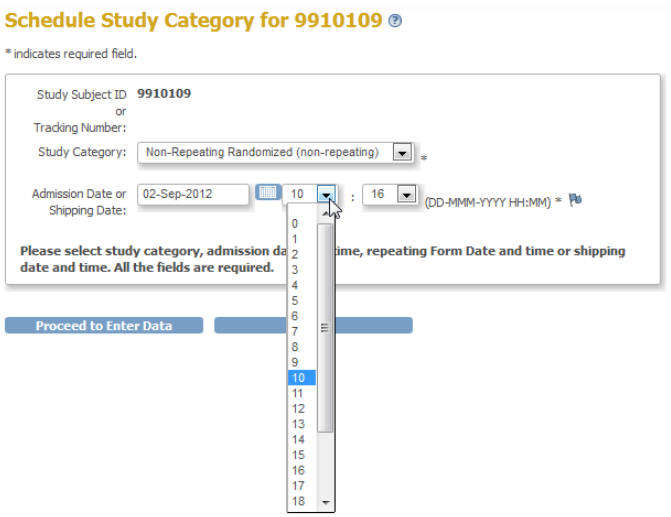
- Once the Study Subject ID is saved, you can continue enrolling a Subject in the correct enrollment category by selecting the category from the drop down list
- Selecting the correct category is important, as explained in the examples earlier, you will only have access to the eCRFs for a Subject, based on the enrollment category selected.
- For a Randomized Subject, select **Non – Repeating Randomized Subjects** from the drop down list as shown.
- This will make the eCRFs for a Randomized Subject available for data entry.

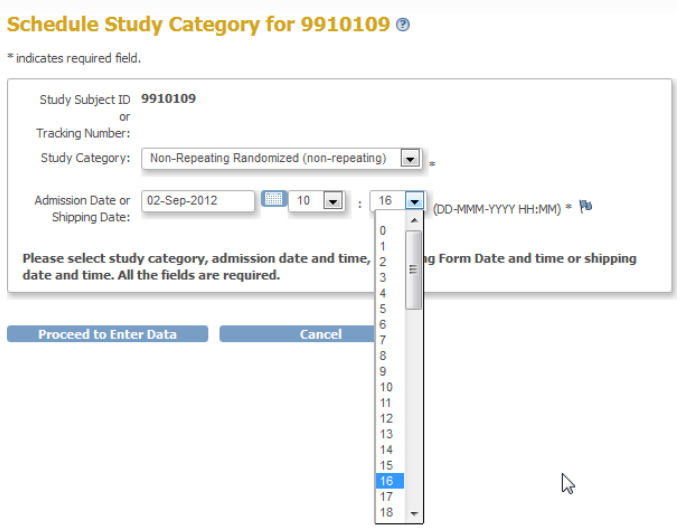
Add a Subject Randomized



- Enter the date by clicking once on the calendar icon to the right of the date input box.
  - The date must be in **DD-MMM-YYYY** format

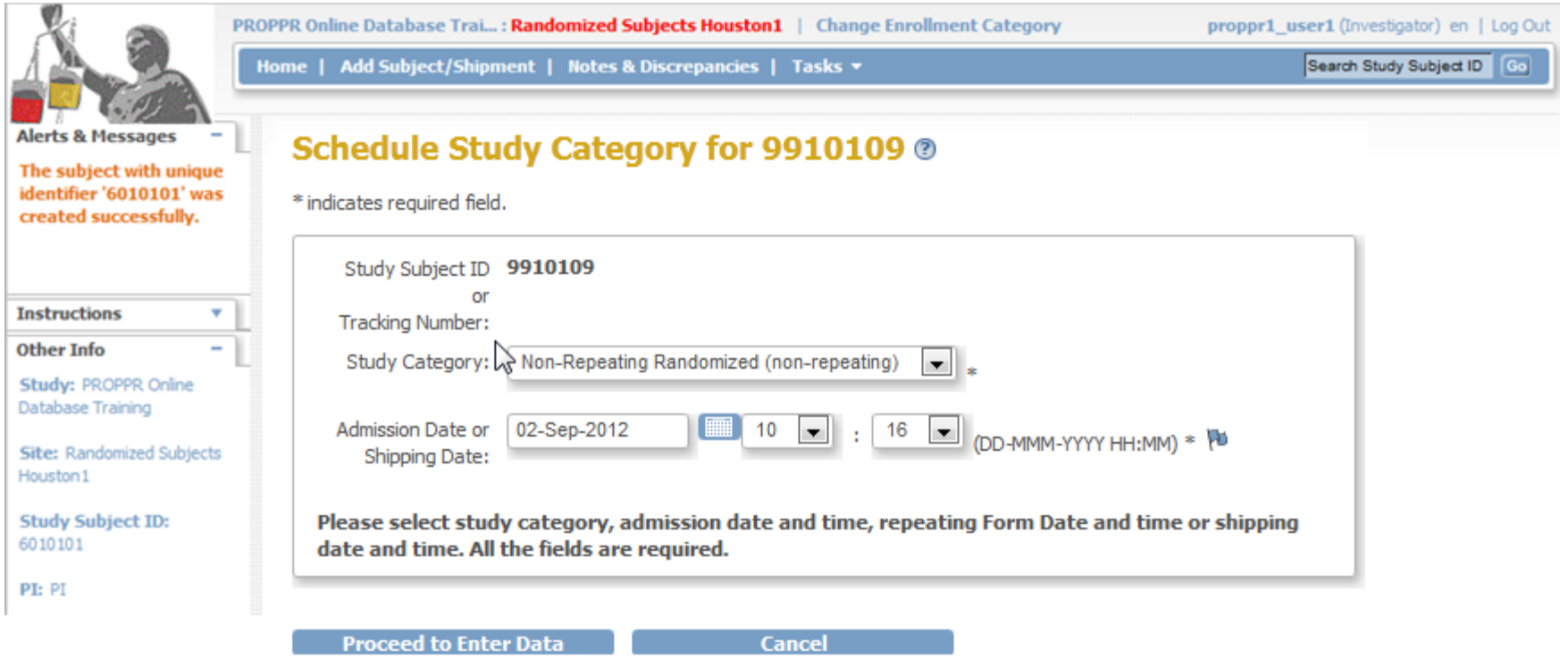
Add a Subject Randomized Subject





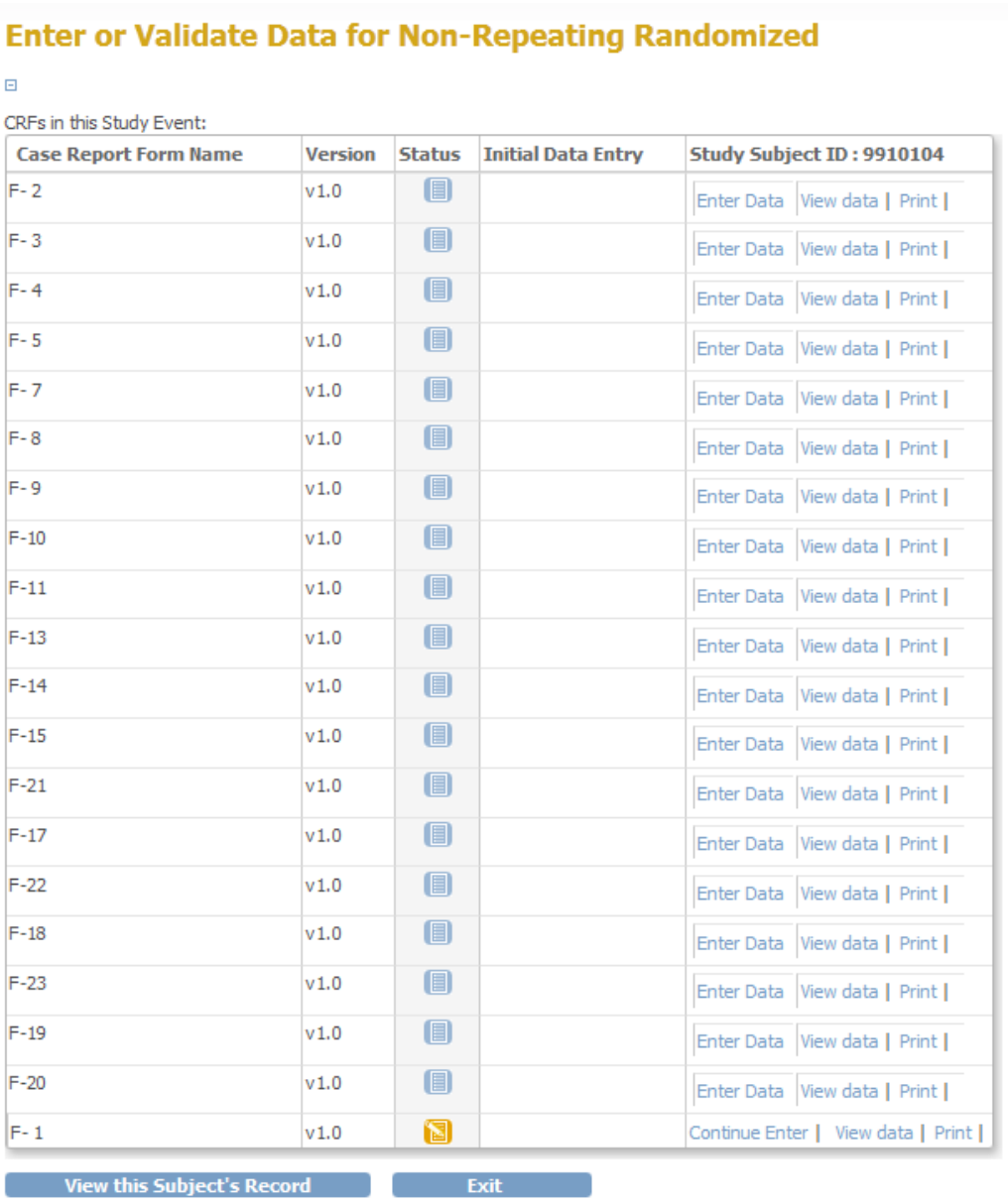
- Enter time from the drop down list provided
  - The time must be in **HH:MM** format

Add a Subject Randomized Subject



- Study CRF – make sure it matches enrollment category in **red**
- Once you have selected the correct enrollment category and have entered the date and time, you can click once on Proceed to Enter Data, to view which eCRFs are available for data enter.

Add a Subject Randomized Subject



Enter or Validate Data for Non-Repeating Randomized

CRFs in this Study Event:

Case Report Form Name	Version	Status	Initial Data Entry	Study Subject ID : 9910104
F- 2	v1.0			Enter Data | View data | Print |
F- 3	v1.0			Enter Data | View data | Print |
F- 4	v1.0			Enter Data | View data | Print |
F- 5	v1.0			Enter Data | View data | Print |
F- 7	v1.0			Enter Data | View data | Print |
F- 8	v1.0			Enter Data | View data | Print |
F- 9	v1.0			Enter Data | View data | Print |
F-10	v1.0			Enter Data | View data | Print |
F-11	v1.0			Enter Data | View data | Print |
F-13	v1.0			Enter Data | View data | Print |
F-14	v1.0			Enter Data | View data | Print |
F-15	v1.0			Enter Data | View data | Print |
F-21	v1.0			Enter Data | View data | Print |
F-17	v1.0			Enter Data | View data | Print |
F-22	v1.0			Enter Data | View data | Print |
F-18	v1.0			Enter Data | View data | Print |
F-23	v1.0			Enter Data | View data | Print |
F-19	v1.0			Enter Data | View data | Print |
F-20	v1.0			Enter Data | View data | Print |
F- 1	v1.0			Continue Enter | View data | Print |

View this Subject's Record | Exit

- **eCRF 1 – eCRF 23**
- These eCRFs are available for data entry for a Randomized Subject:
- eCRF 1 – status is data entry started, represented by the orange icon, this is the first eCRF for data entry
- **F-6, F-12, F-16**
  - These are repeating forms. They are accessible from the Subject Matrix. A date and time must be entered for each occurrence of a form.
- All of the others,
  - are ready for data entry and are represented by a blue icon.

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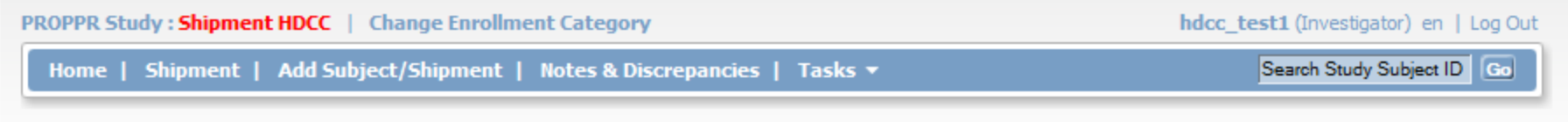
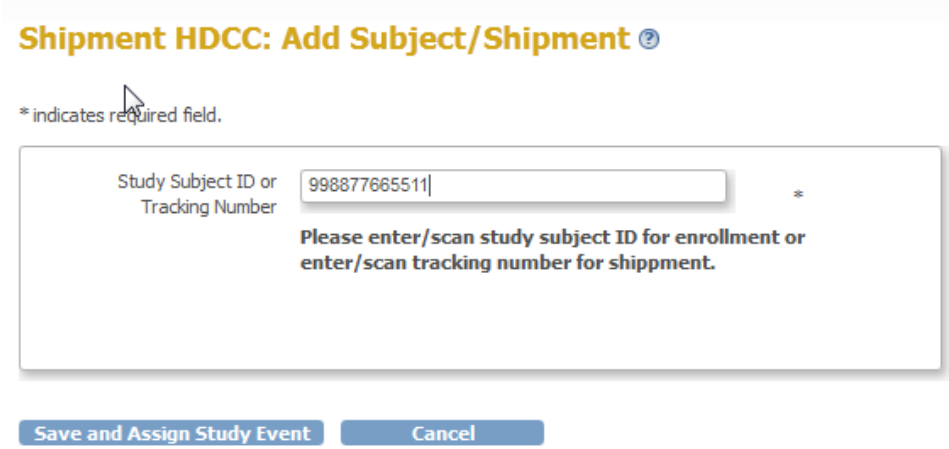
ADD - SHIPMENT

Add a Shipment Category

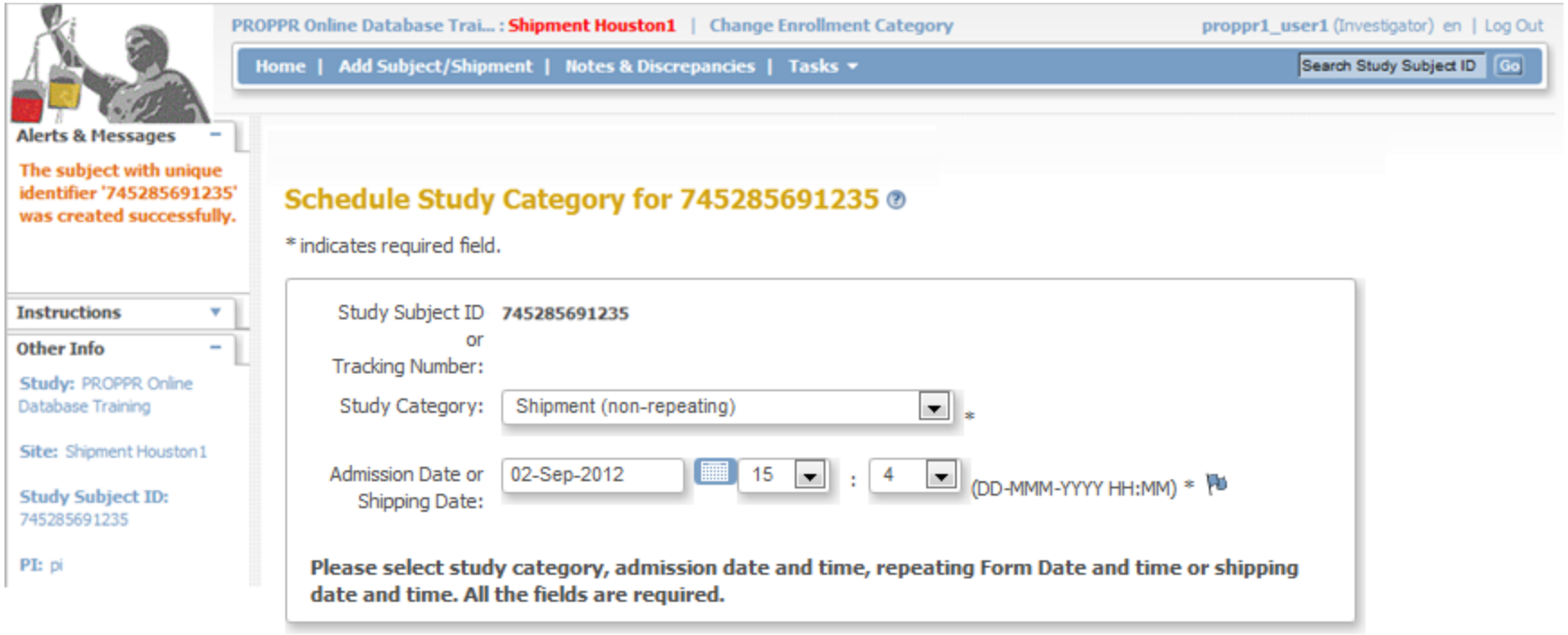


- Click once on the Add Subject link.
- The Add New Subject/Shipment Page appears



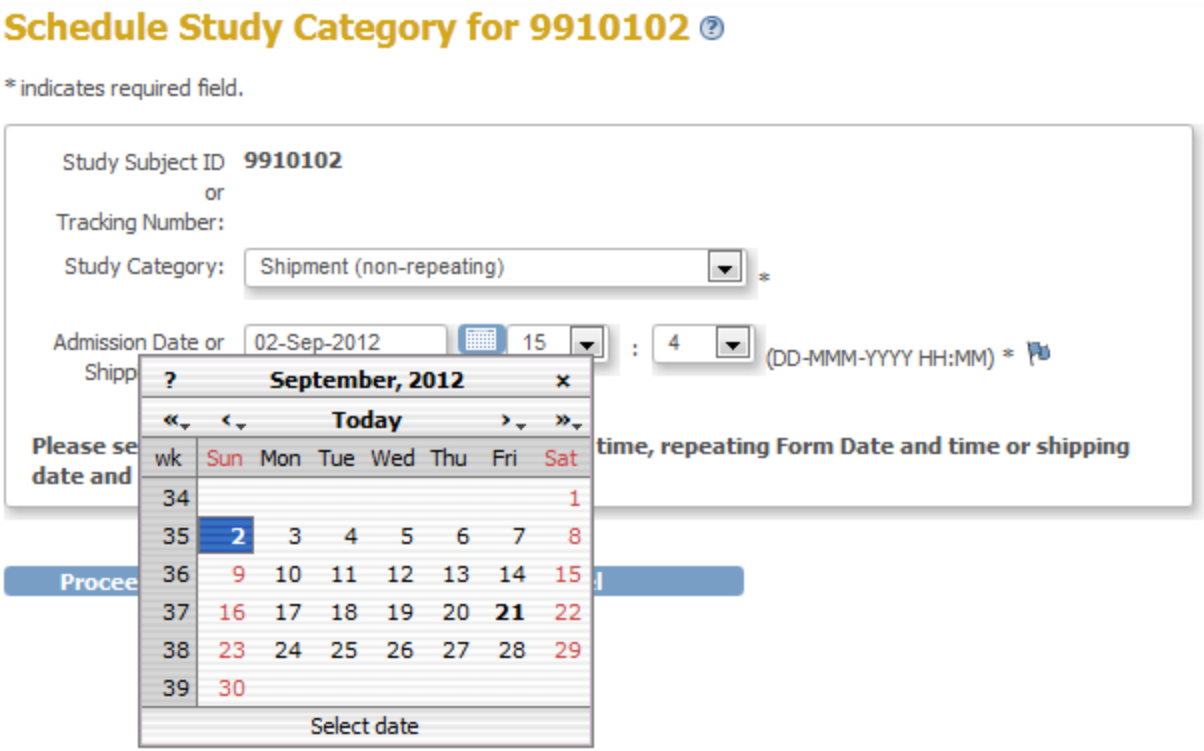
- Before entering the Shipment ID, make sure that the current enrollment category in **red**, is correct. If it is correct, enter the shipment ID and click once on Save and Assign Study Event to add the new shipment ID to your site.
- If the category is not correct, click cancel and then change the current enrollment category to the correct one.
- **If you assign a shipment ID to the wrong enrollment category, you will not have access to the Shipping Log and will not be able to change the enrollment category for that shipment without contacting the HDCC**

Add a Shipment



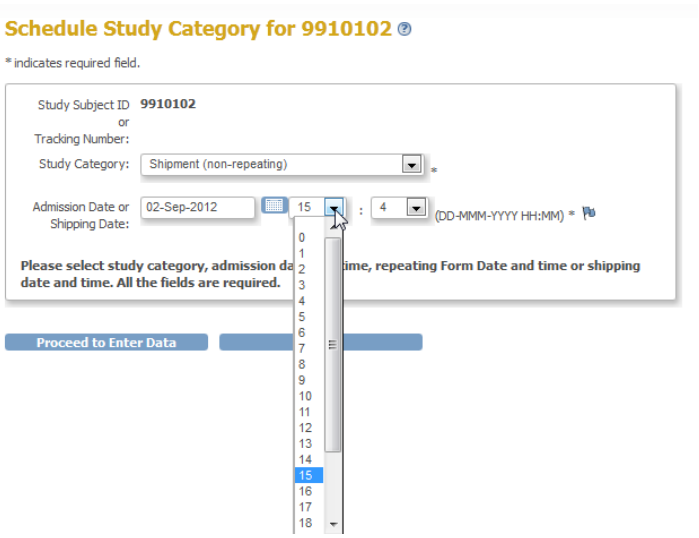
- Once the Shipment ID is saved, you can continue enrolling a shipment in the correct enrollment category by selecting the category from the drop down list
- Selecting the correct category is important, as explained in the examples earlier, you will only have access to the eCRFs for a shipment, based on the enrollment category selected.
- For a Shipment, select Shipment from the drop down list as shown.
- This will make the Shipping Log for a Shipment available for data entry.

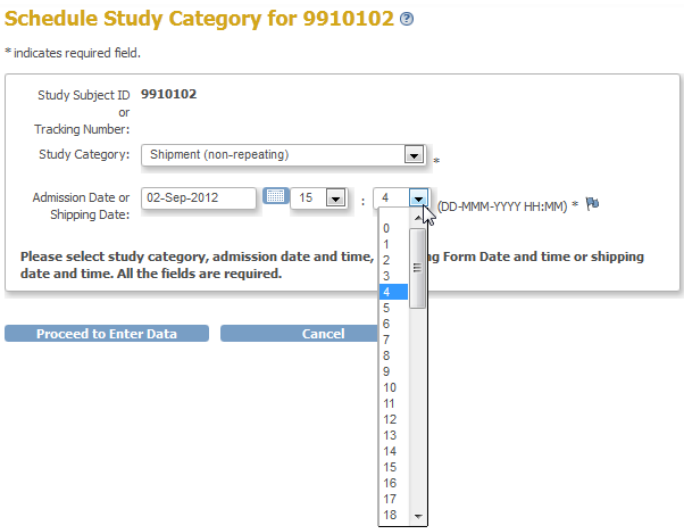
Add a Shipment



- Enter the date by clicking once on the calendar icon to the right of the date input box.
  - The date must be in **DD-MMM-YYYY** format

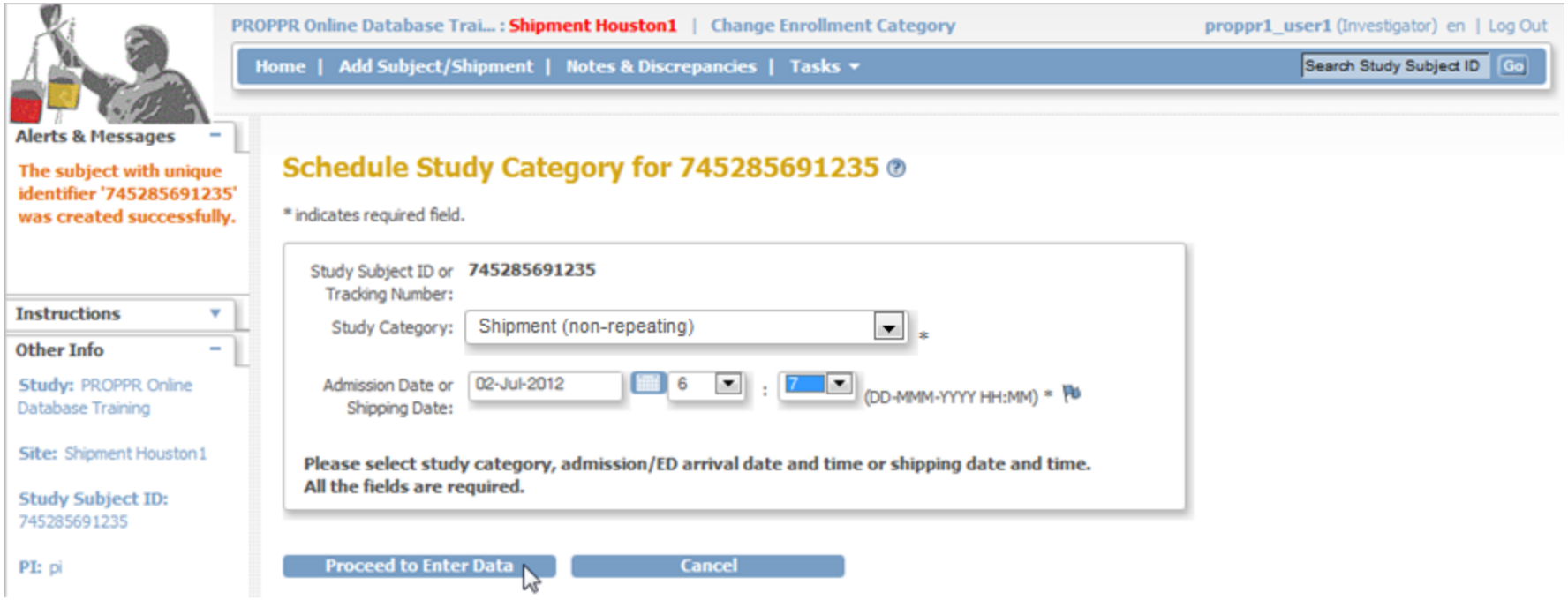
Add a Shipment





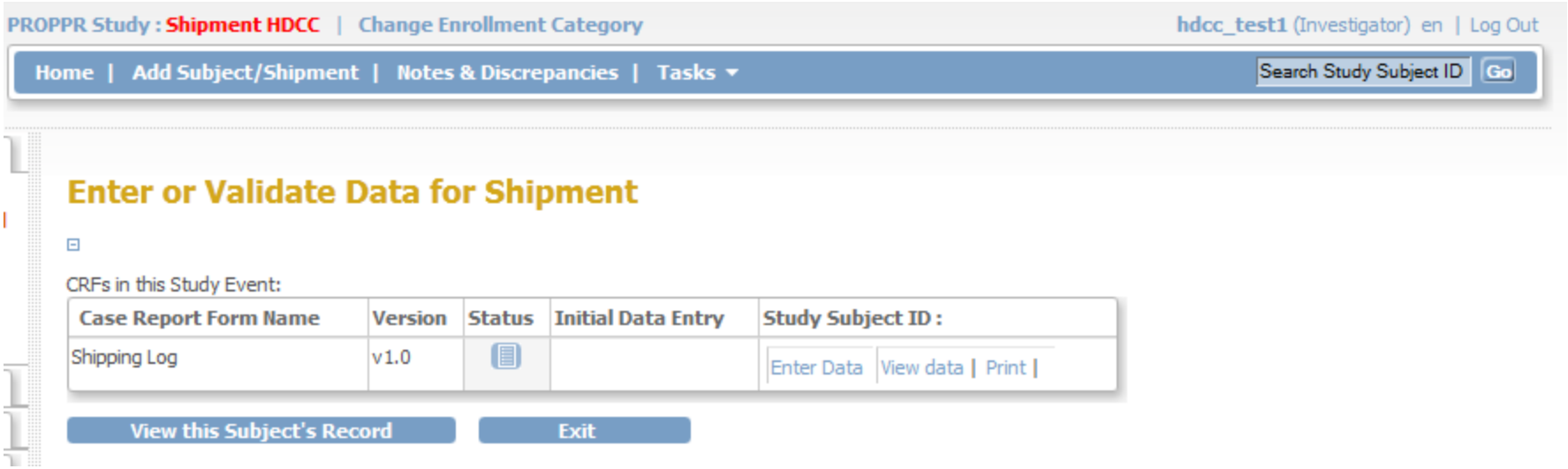
- Enter time from the drop down list provided
  - The time must be in **HH:MM** format

Add a Shipment



- Study CRF – make sure it matches enrollment category in **red**
- Once you have selected the correct enrollment category and have entered the date and time, you can click once on Proceed to Enter Data, to view which eCRFs are available for data enter.

Add a Shipment



- **Lab Shipment Log**
- Only this shipping log is available for data entry for a Shipment:

Review – Steps to Add a New Subject

- The current category is in **red** at the top of the page
- Depending on the current category, you will only be able to enter data into eCRFs that are available for that category
  - Randomized – eCRFs (1 – 23) **6,12,and 16 are repeating forms**
  - Screen Failure – eCRFs (1,2,4,12,14,22,23,24) **12 is a repeating form**
  - Shipment – Shipping Log
- To add a new Subject, first make sure the current enrollment category,

  Randomized, Screen Failure or Shipment

  Is the correct category, then click once on the Add Subject/Shipment link
- Scan the barcode from the paper CRF label to enter the 7 digit Study ID, again make sure the enrollment category is correct and click Save/Assign Study Event
- Select the enrollment category from the Study CRF drop down list
- Select the date and time of Admission/ED arrival
- Click once on Proceed to Enter Data
- The screen will display the eCRFs that are available for data entry
  - eCRF 1 – eCRF 23 for Randomized Subjects
  - eCRF (1,2,4,12, 14,22,23,24) for Screen Failure Subjects
  - Shipment – Shipping Log

If you enroll a Subject in the wrong category.

- You will not have access to the correct eCRFs if the Subject is in the wrong category.
- **Do Not** try to **remove** the subject from the study.
  - This will not remove the Subject from the Study.
  - Once you have entered a Subject ID, that Subject ID cannot be used again as all Subject IDs have to remain unique.
- Do not begin entering data for this Subject without contacting the HDCC. If you enter data in eCRFs within the wrong category, this data could be lost and have to be reentered.
- **The only way to get the Subject in the correct category is to contact the HDCC.**

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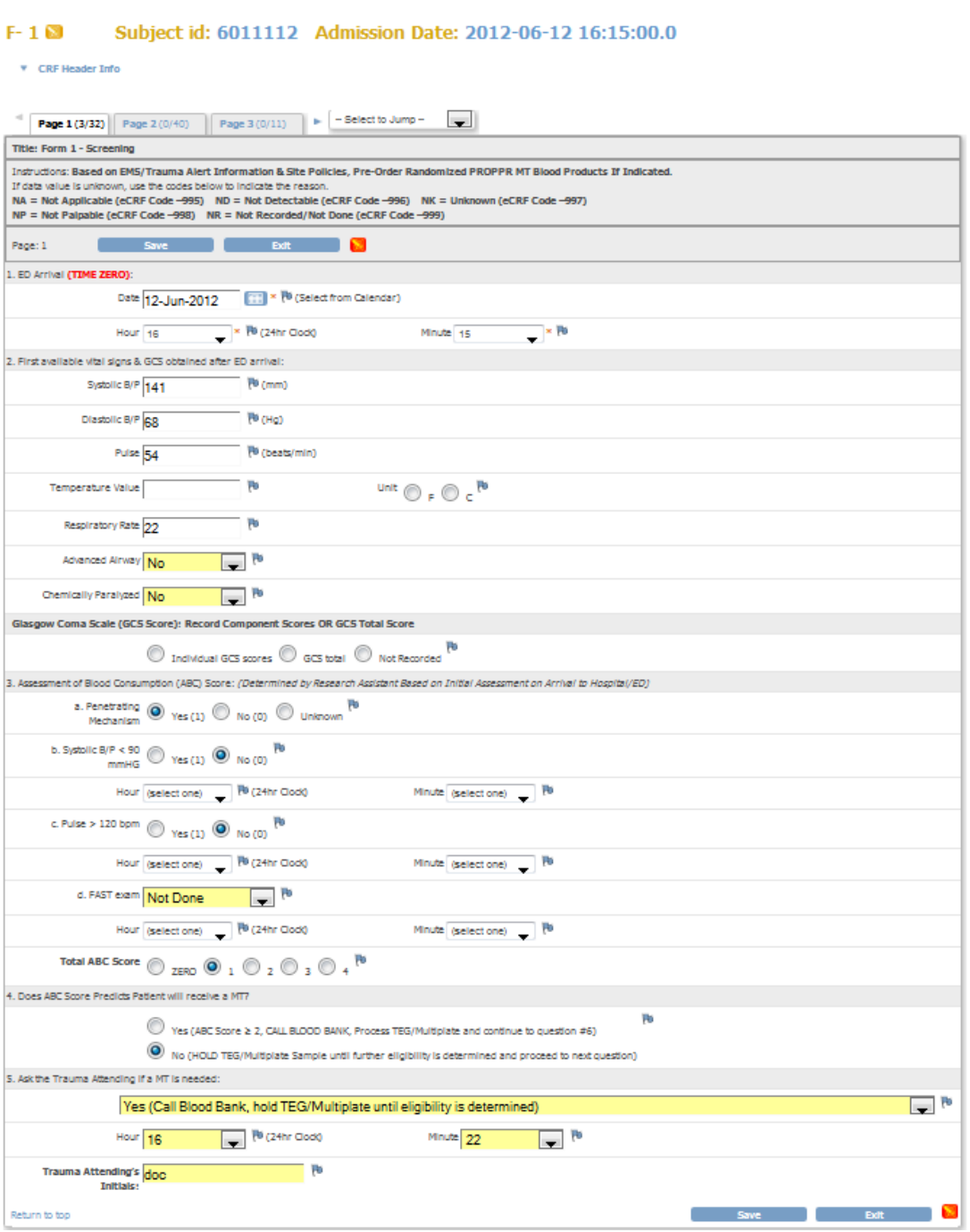
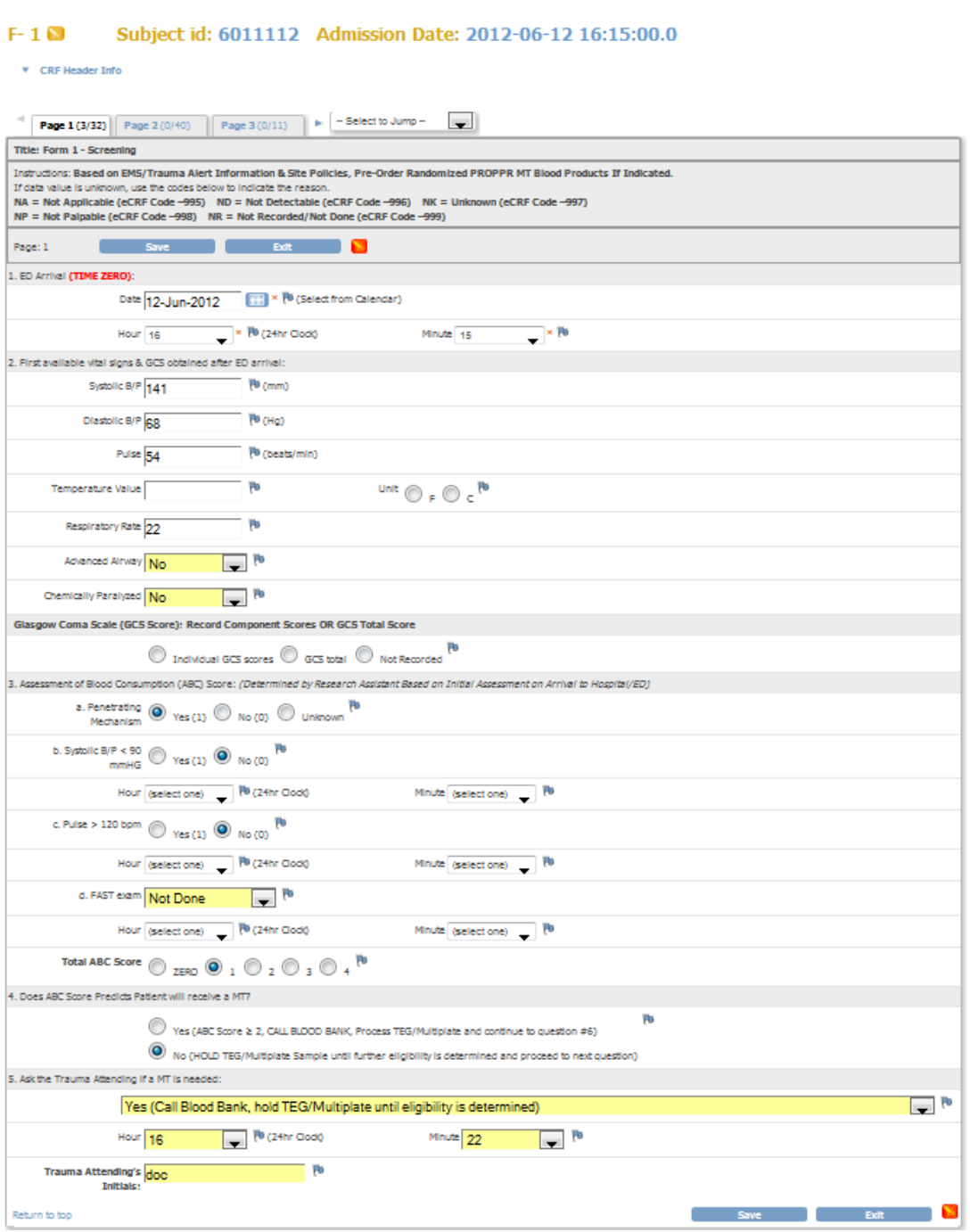
ENTER DATA INTO AN eCRF

eCRF Layout



- The layout of an eCRF is:
  - Current Section Tab
  - Other Section Tab
  - Section Drop Down List
  - Title
  - Instructions
  - Body of Current Section
  - Question Headers
  - An asterisk in orange * indicates a required field. You cannot save the eCRF without entering the data for a required field.

eCRF Layout



- Each Item in a section is numbered, i.e. on the Current Section Tab, 3/32 indicates that there are 32 elements to complete for this section.
- Once you have completed the elements for the current section, you need to click Save to proceed to the next section.
- PROPPR Online Database will automatically load the next section

Codes for missing data

	CRF code	eCRF Code
Not Applicable	NA	–995
Not Detectable	ND	–996
Unknown	NK	–997
Not Palpable	NP	–998
Not Recorded/Not Done	NR	–999

- Use these codes for missing data.
- These codes are in the Manual of Instruction for the CRFs and located below the Table of Contents for the CRFs
  - Use the **CRF code** for the paper forms
  - Use the **eCRF code** when entering data in PROPPR Online Database
    - Must put a (-)minus sign before numeric value

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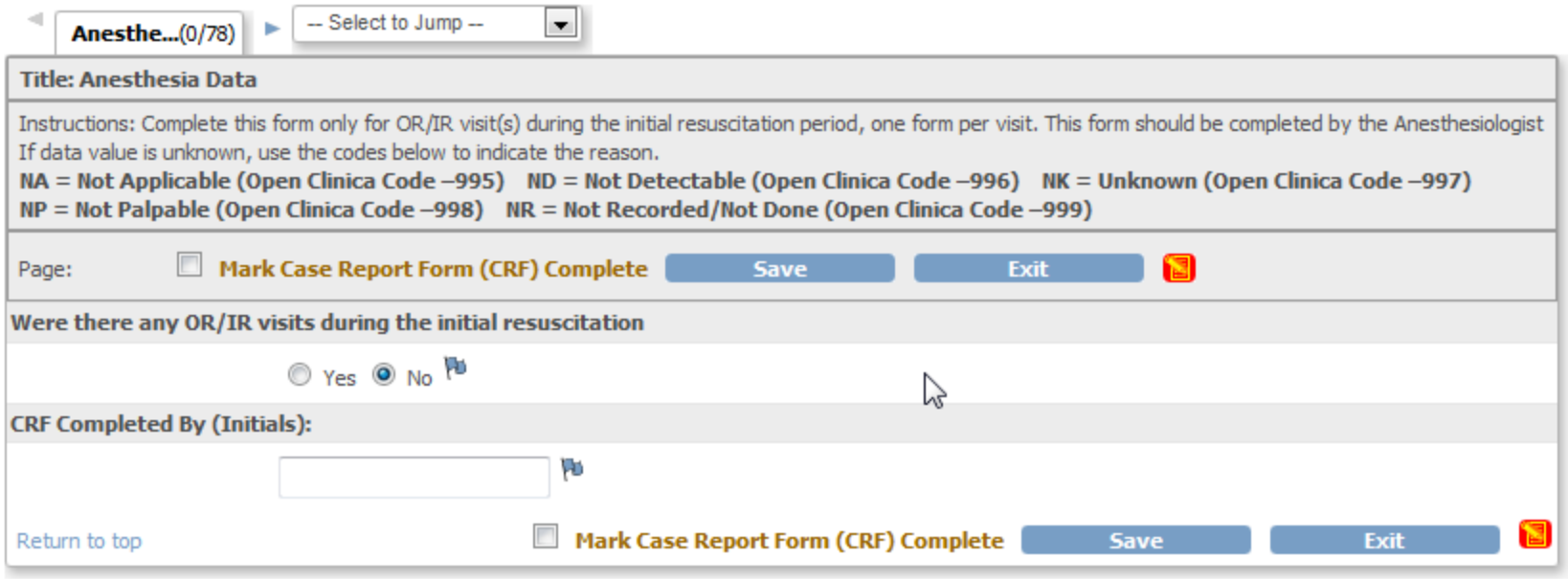
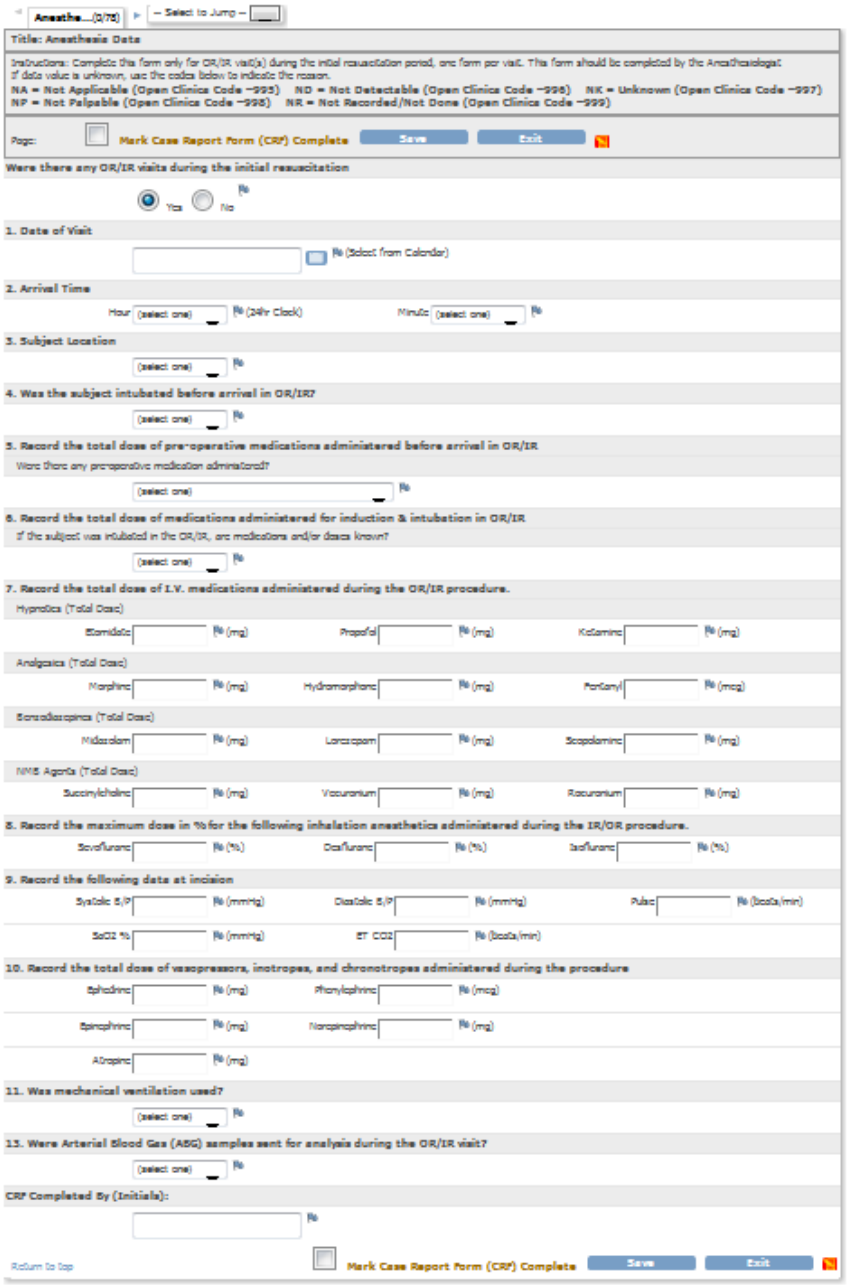
FORM HIDE/SHOW LOGIC

eCRF Hide/Show Logic



- Some Forms will Hide/Show questions based on the value of a question's answer.
- Example: F-15 Anesthesia Record
  - Based on the value of the first question "Were there OR/IR visits during the initial resuscitation" Yes/No
  - If No, the form is complete and there is no other form data to enter

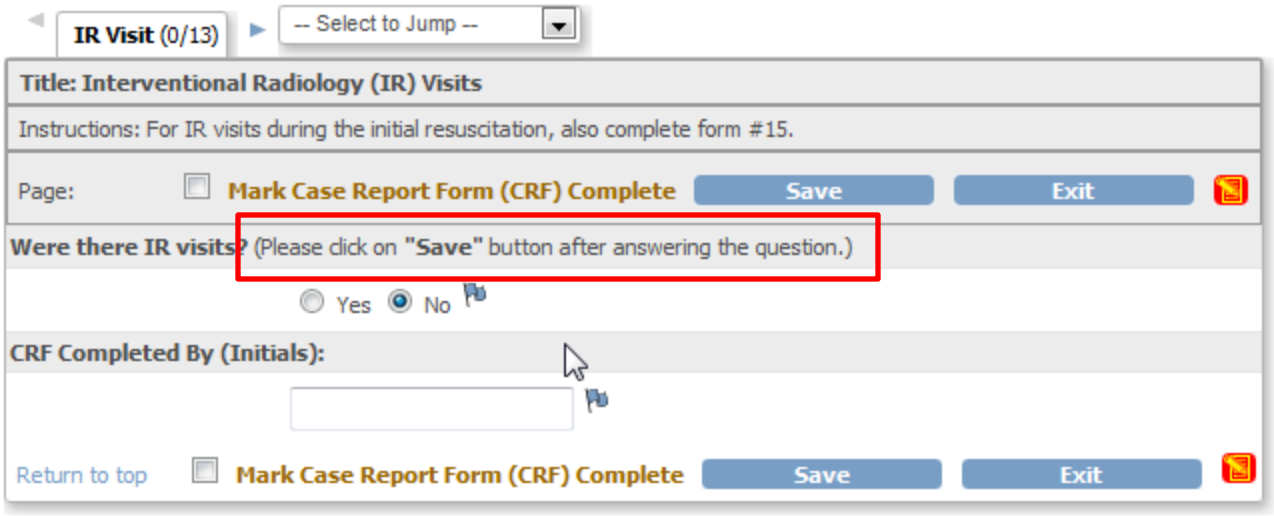
eCRF Hide/Show Logic



- **F-15 Example continued**
- If Yes is selected, then resulting questions must be answered.

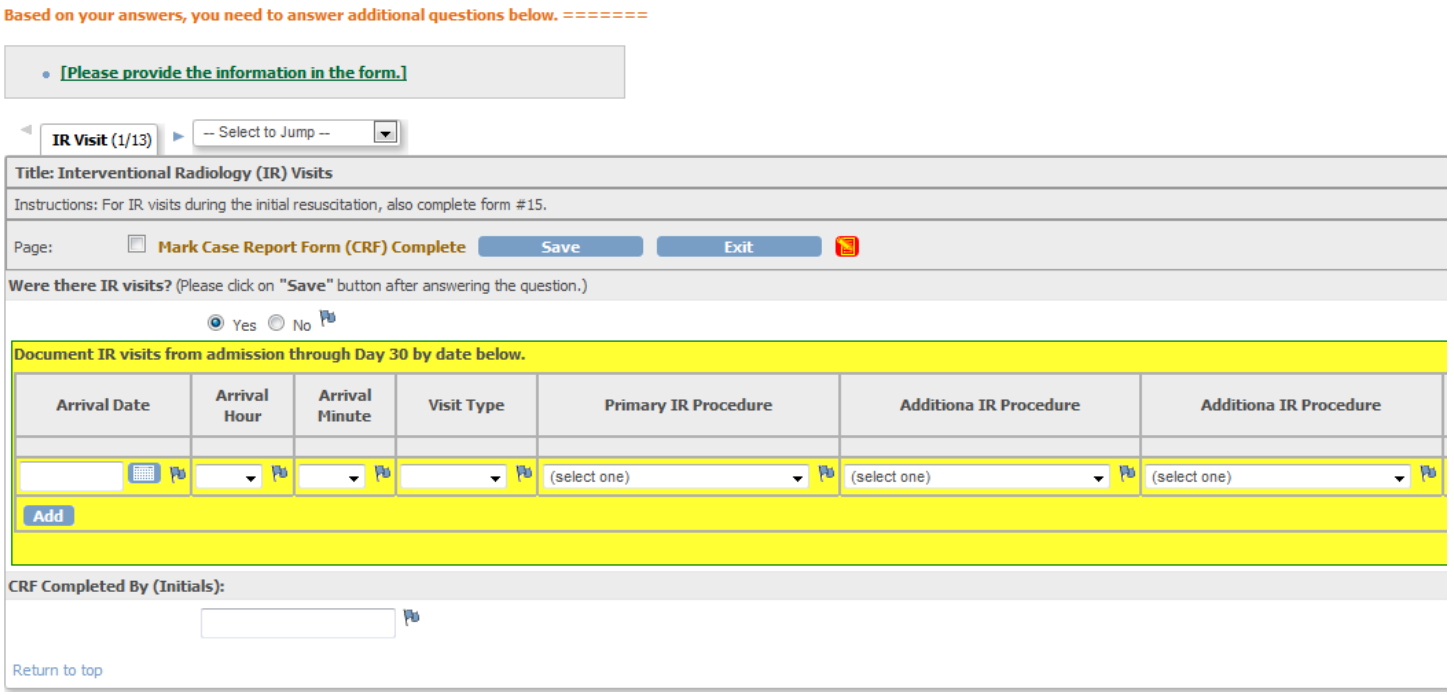
- This is not the only type of Hide/Show Logic within forms.
- Some Grouped Items will have Hide/Show logic as well.

eCRF Hide/Show Logic



- Grouped Item Example
- F- 11 – Interventional Radiology Visits
- This form has grouped items, **The instructions for the first question tell you to click once on the Save button after answering**.
- Answering No and then clicking Save will not show any other questions and the form is complete.

eCRF Hide/Show Logic



- F-11 Example continued
- If Yes is selected, then resulting questions must be answered.
- **The Grouped Items are presented only after the initial question is answered and the Save button is pressed.**
- The eCRFs that begin with this Hide/Show logic are
  - **F-8,F-9,F-10,F-11,F-14,F-18,F-19, and F-22**

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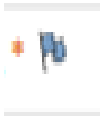
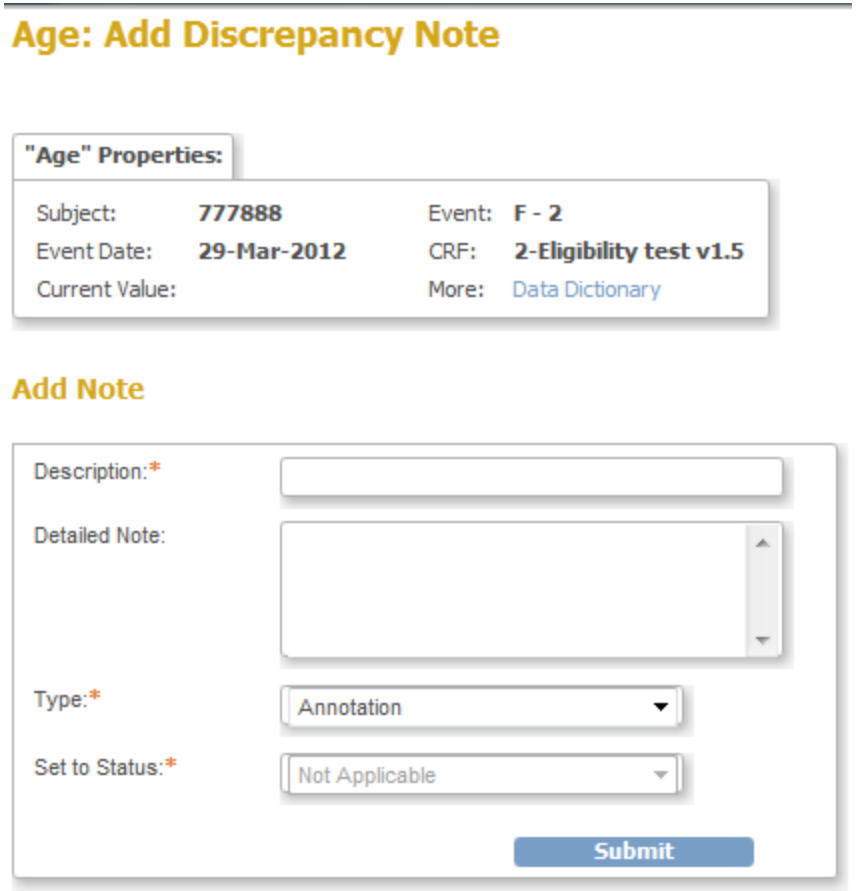
DISCREPANCY NOTES

PROPPR Discrepancy Notes

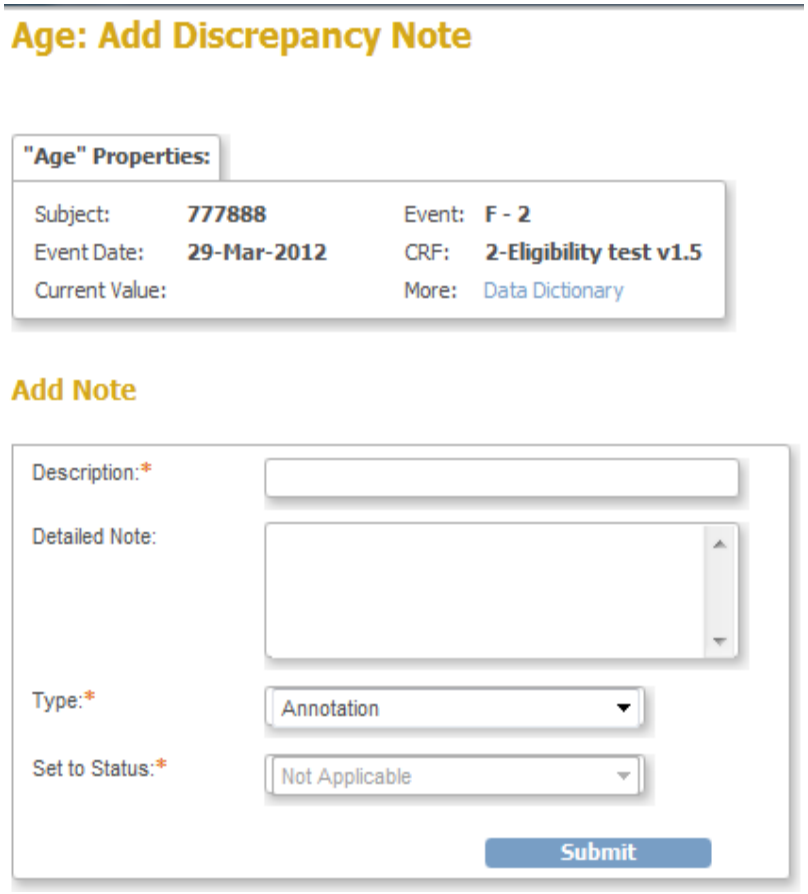
- A Discrepancy Note is associated with a single data element, usually a eCRF Item.
- Once a Discrepancy Note is created, it cannot be deleted.
- To use Notes and Discrepancies, your browser must have:
  - JavaScript enabled
  - Pop-up blockers disabled
- A Discrepancy Note has four key properties, which the user assigns when creating the note:
  - Note Type
  - Status
  - Description
  - Detailed Note
- After the Discrepancy Note has been created, you cannot change the Note Type.





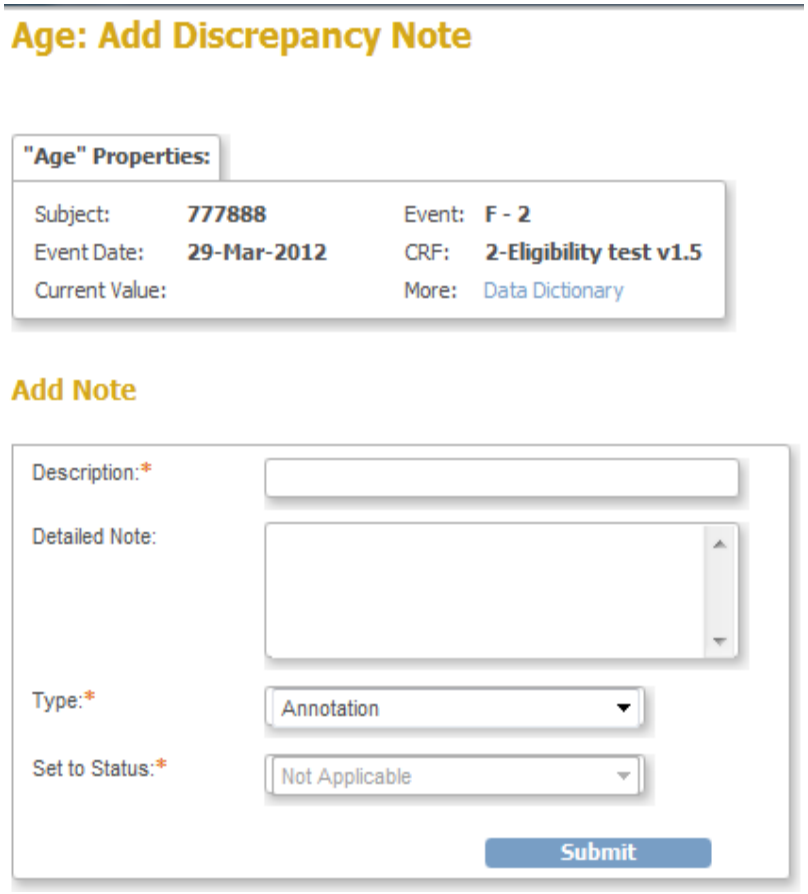
PROPPR Discrepancy Notes – Note Types

- PROPPR Online Database has 4 Discrepancy Note Types:
  - Failed Validation Check
  - Query
  - Reason for Change
  - Annotation



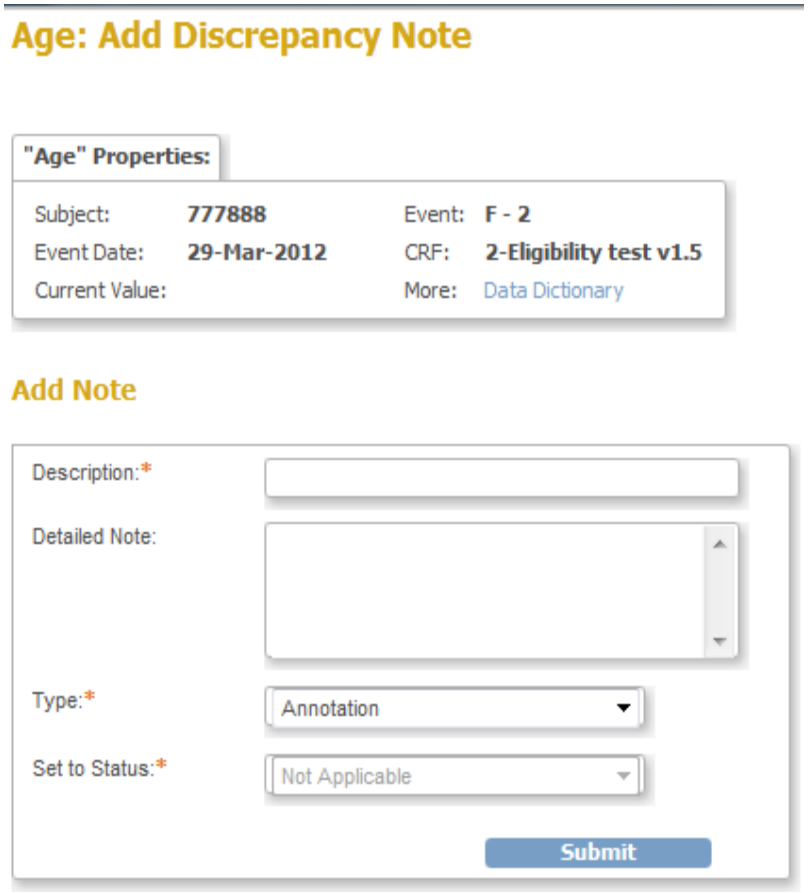
PROPPR Discrepancy Notes – Note Types

- Failed Validation Check- is for data that does not comply with expected values. A Failed Validation Check Discrepancy Note can be created in these ways:
  - A user entering data can manually create
  - PROPPR Online Database can **automatically generate** this Note. PROPPR Online Database first displays a warning message. **If the user does not change the value to one that conforms to the expected values for the Item**, it creates a Failed Validation Check Discrepancy Note.



PROPPR Discrepancy Notes – Note Types

- **Query** - A Query Note Type is used to ask a question about data provided for an Item that seems incomplete or incorrect, even though the item has met all automated edit checks.
- **Reason for Change** - any change made to the eCRF after the eCRF data entry is marked complete requires a Discrepancy Note.
- **Annotation** - Annotation Discrepancy Notes are to make comments or provide information about the data that cannot be adequately represented in the eCRF.



PROPPR Discrepancy Notes – Statuses

The status for a Discrepancy Note provides an indication of who is responsible for the next step. The Discrepancy Note Type determines what status values are allowed. These are the possible values:

- **New :** The initial status for a Query or Failed Validation Check Note Type.
  - **Updated :** Used when responding to a Note, but the response requires further Follow-Up or additional information.
  - **Resolution Proposed :** When a user addresses a Note by fixing a data problem or by explaining why the existing data is correct, the user provides an explanation in a child Note, and sets the status to Resolution Proposed.
  - **Closed :** The final action for a Failed Validation Check or Query Note Type. When a Note has a status of Closed, it cannot be changed in any way. Child Notes cannot be added and the status must remain Closed. Only users with certain Roles can mark a Discrepancy Note as Closed.
- **Not Applicable :** This status is for Reason for Change and Annotation Note Types because no further action is required. The Not Applicable status cannot be used for Failed Validation Check and Query Note Types.

- New :
- Updated :
- Resolution Proposed :
- Closed :
- Not Applicable :

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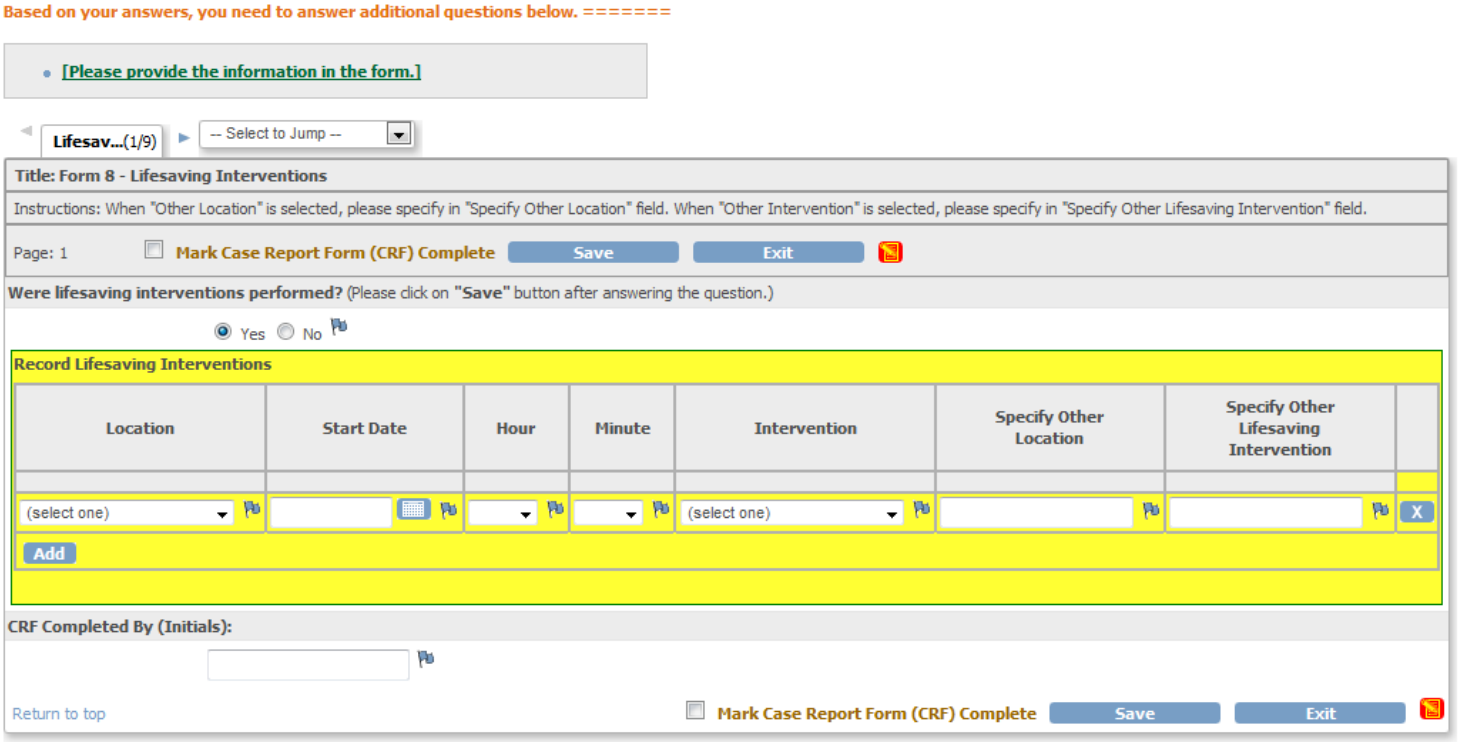
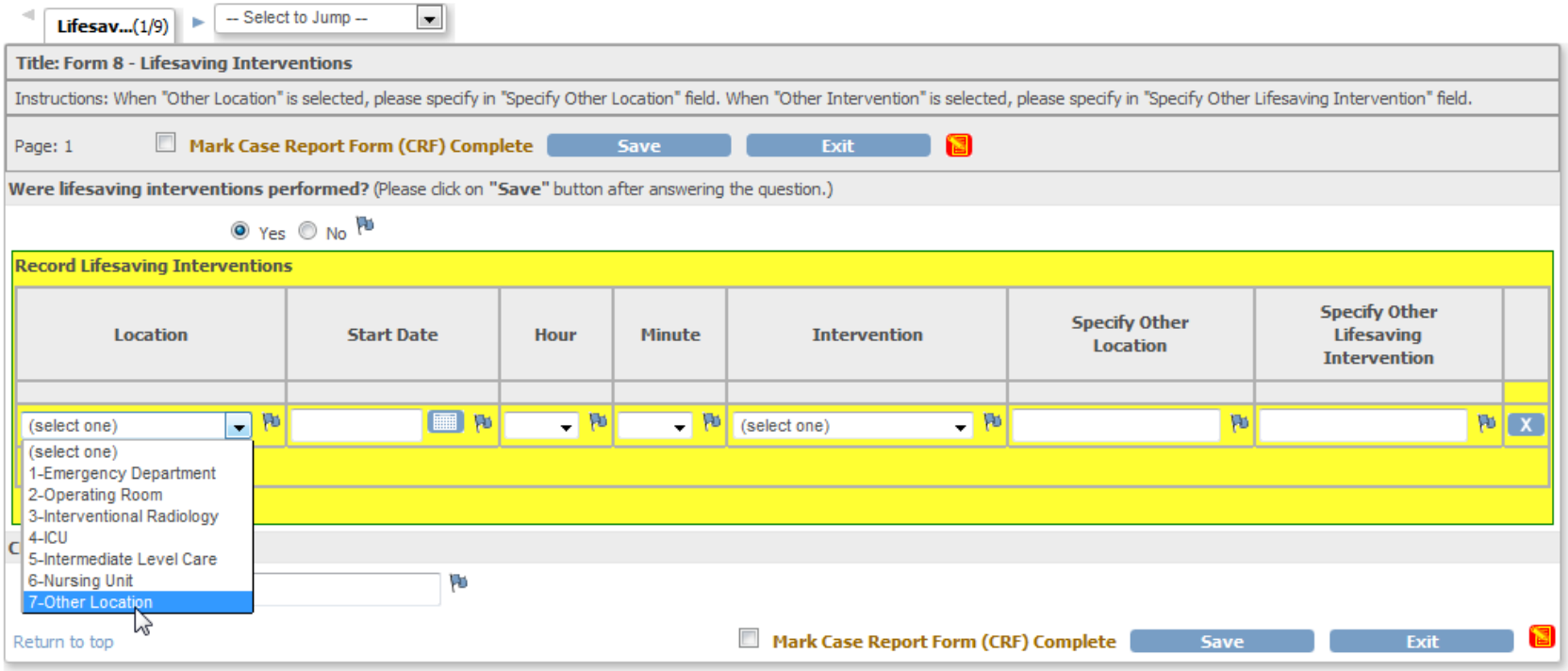
GROUPED ITEMS

Grouped Items



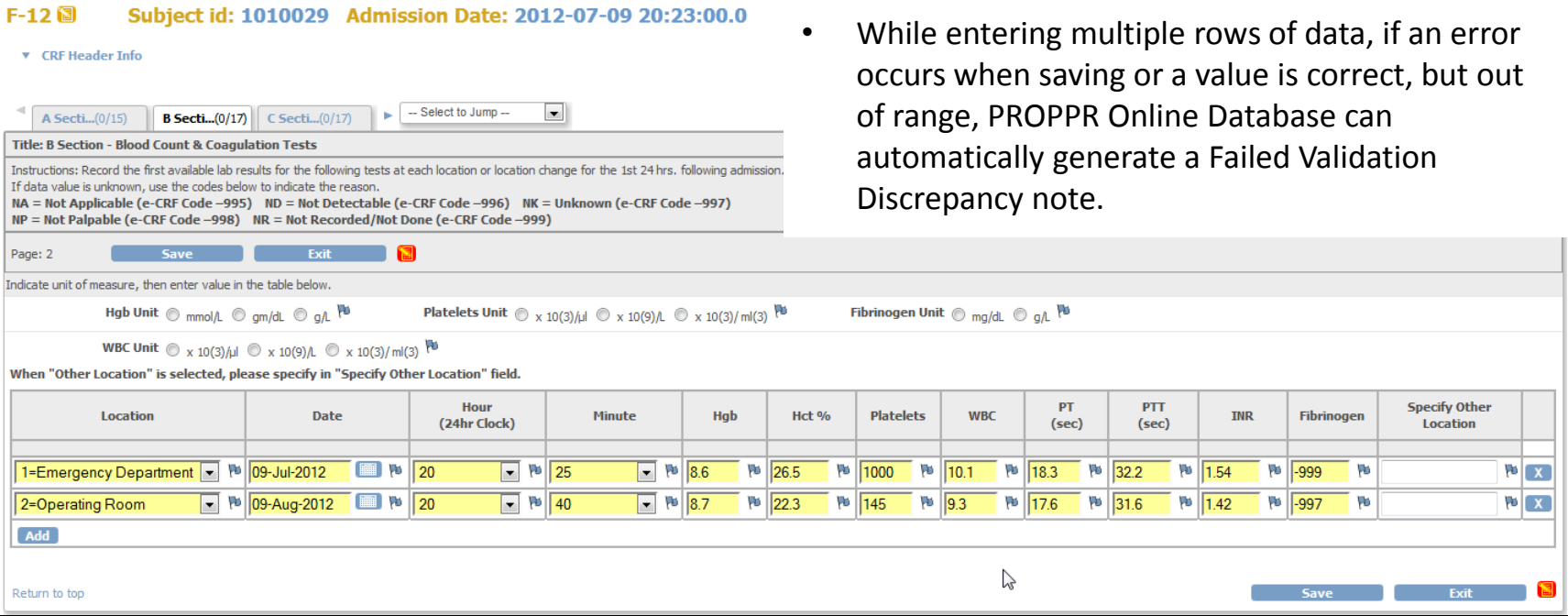
- Grouped Items are those that can repeat several times:
- PROPPR Online Database will present you with one row by default. To add another row, click once on the "Add" button.
- You can add as many rows as necessary.

Grouped Items

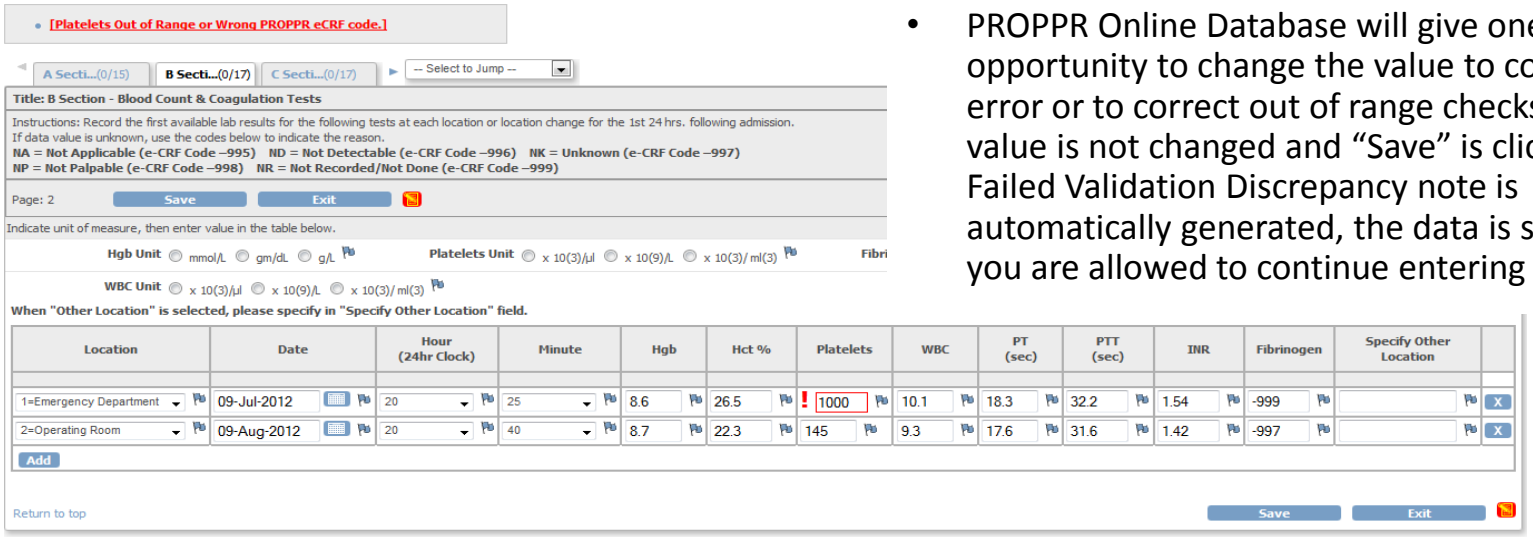


- If “Other” is selected within a grouped item.
- You must then type in the location in the appropriate textbox.
- **Example: F-8 Lifesaving Interventions**
  - Other Location and Other Intervention
  - There is a textbox for each “Other” option on the grouped item row.
  - Make sure to put the appropriate information in the correct textbox.

Grouped Items – discrepancy notes



- While entering multiple rows of data, if an error occurs when saving or a value is correct, but out of range, PROPPR Online Database can automatically generate a Failed Validation Discrepancy note.



- PROPPR Online Database will give one opportunity to change the value to correct an error or to correct out of range checks. If the value is not changed and “Save” is clicked again, a Failed Validation Discrepancy note is automatically generated, the data is saved and you are allowed to continue entering data

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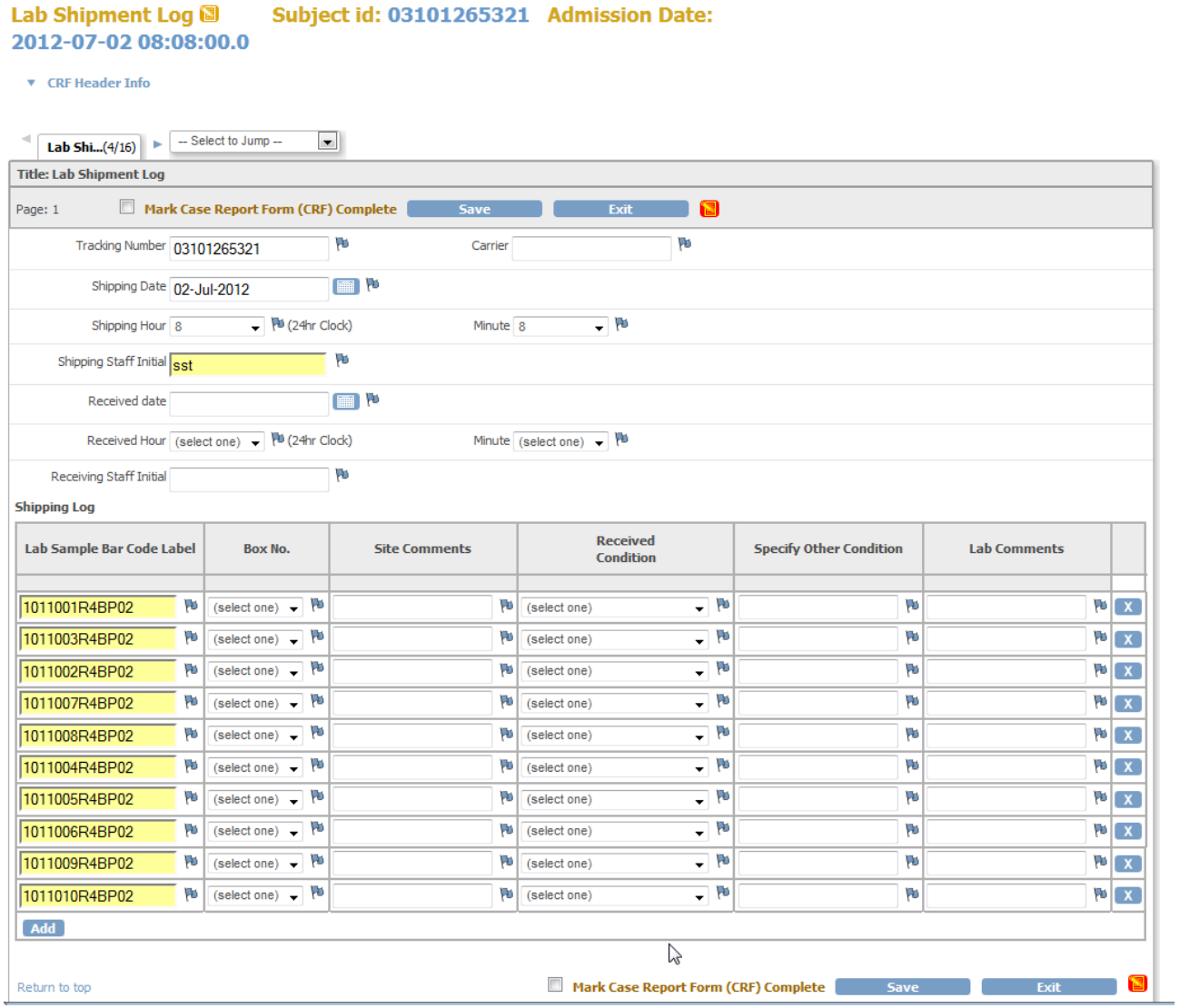
PRINTING THE SHIPPING LOG

Printing the Shipping Log



The Shipping Log can be printed following the Instructions below:

- Make sure to always print the Shipping Log in **Landscape page orientation**. If not, information can be truncated and left off of the printout.

To Print the schedule In FireFox:

- Click on the Firefox menu
- Point cursor to Print option
- Click once on Print
- A copy of the schedule will print.

To Print the schedule from Internet Explorer:

- Click on the File
- Click once on Print

Or

- Use the keyboard shortcut: Ctrl+P to print
- A copy of the schedule will print.

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ADDITIONAL NOTES

Additional Notes

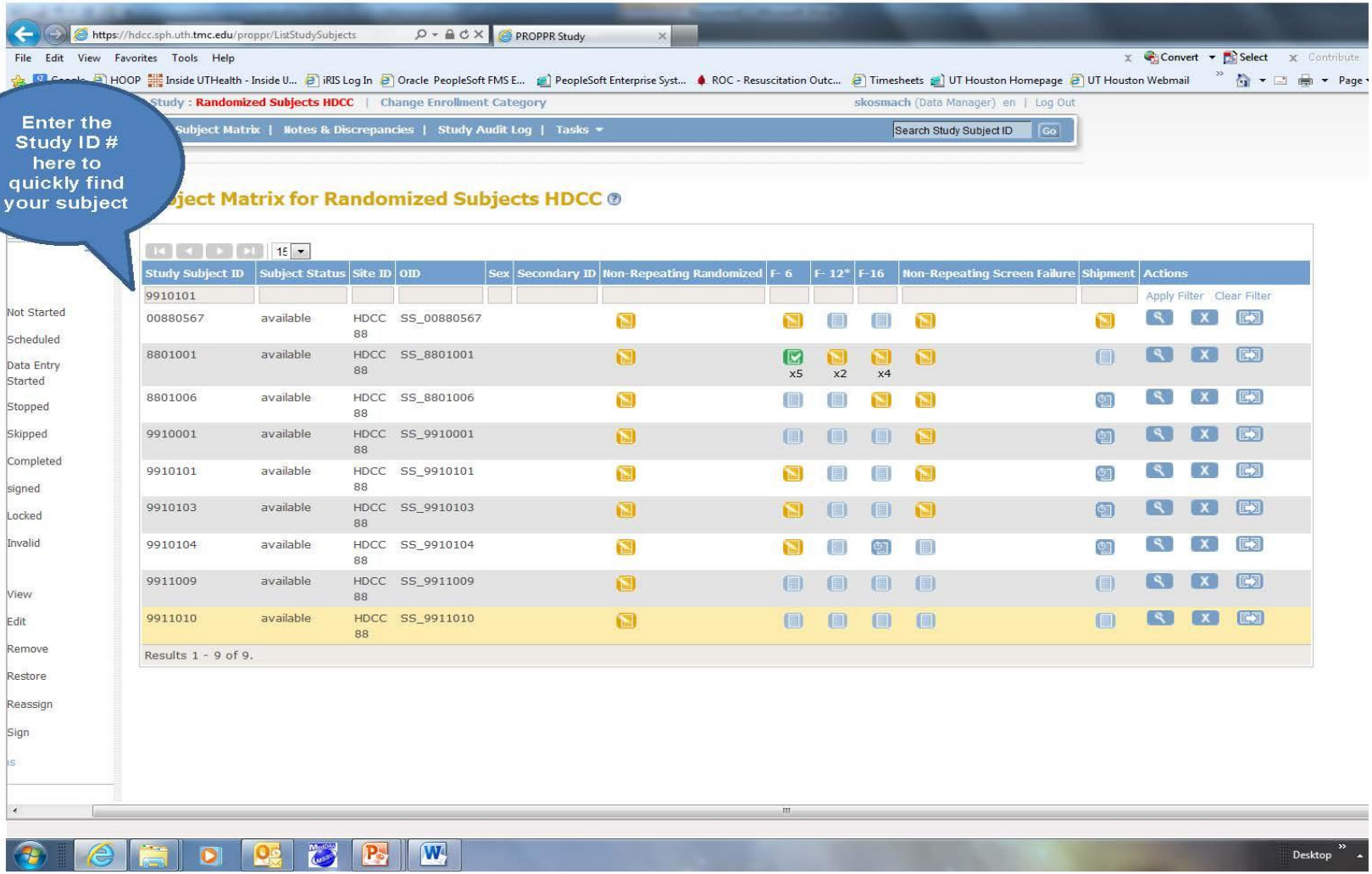
- **Which browser to use?**
- **These are the only browsers supported by OpenClinica**
  - **The use of a browser other than the ones listed below can lead to loss of data:**
  - **Internet Explorer 7.0+**
    - JavaScript enabled and pop-up blocker turned off
  - **Internet Explorer 8.0+**
    - JavaScript enabled and pop-up blocker turned off
  - **Mozilla Firefox 3.6+**

- **<u>Google Chrome is not a supported browser.</u>**

Additional Notes

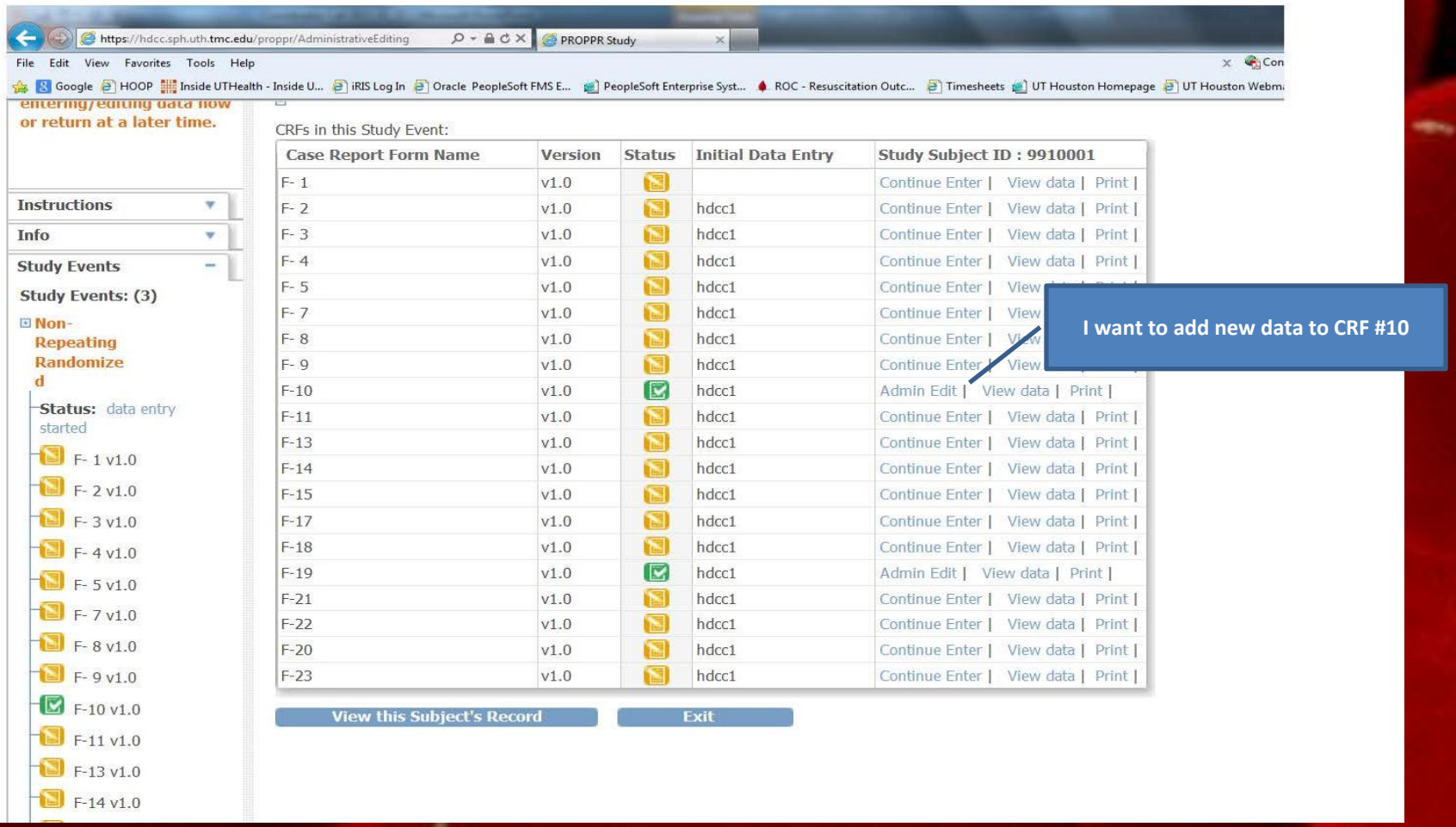
- **Safe usage tips**:
  - **Only use the navigation buttons within PROPPR Online Database application:**
    - Using your browser navigation buttons may lead to loss of data
    - Before navigating away from the current page, make sure to save the current page first.
  - **When saving data for a form, only click <u>once</u> on Save.**
    - Wait until the next screen appears.
      - The more items entered on a form, the longer PROPPR Online Database takes to save items.

OpenClinica Tips: Finding Your Subject



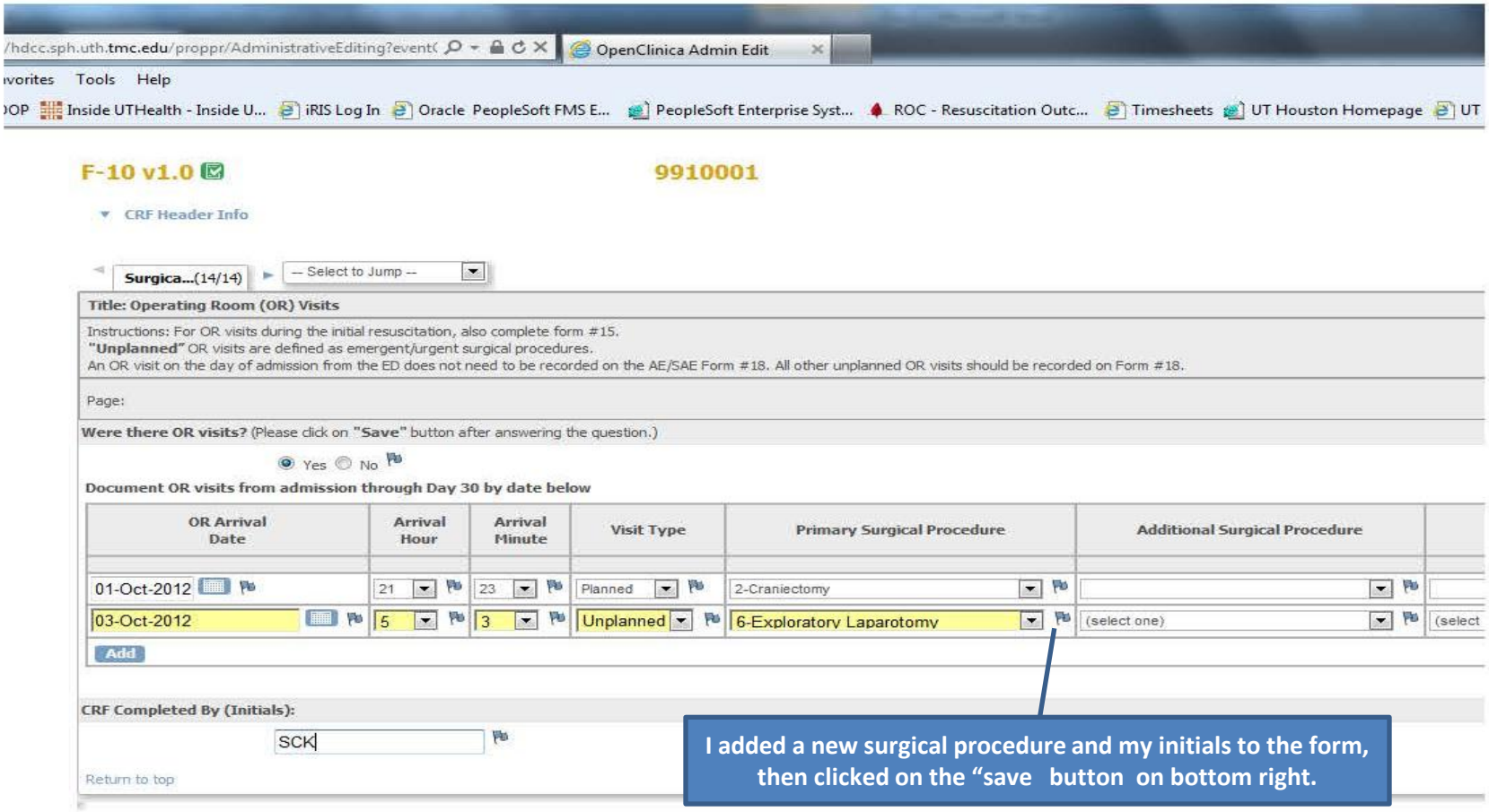
OpenClinica Tips: Correcting "Saved Complete" CRF's

Select "Administrative Edit" to open the form.



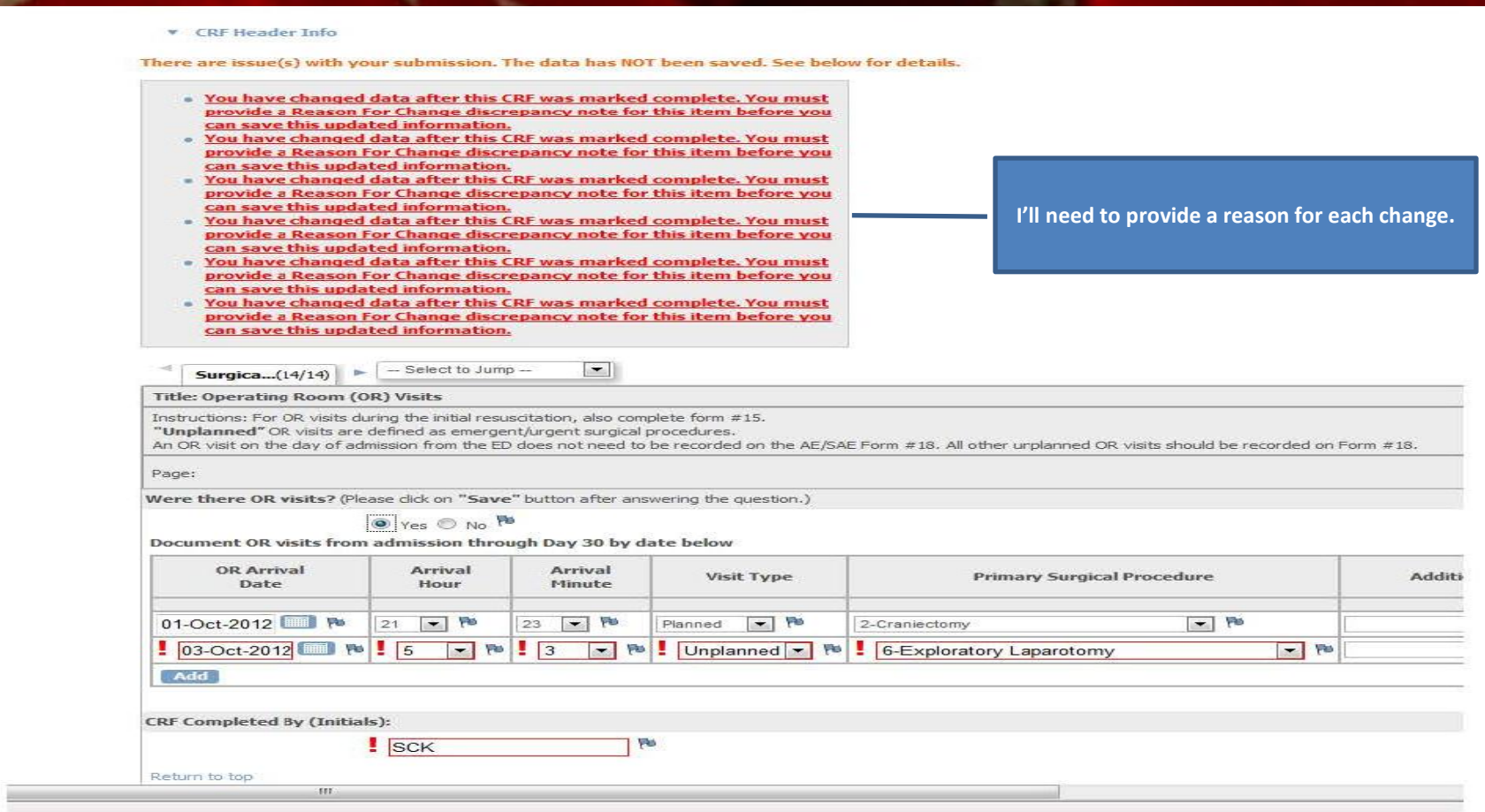
OpenClinica Tips: Correcting "Saved Complete" CRF's

Make Form Corrections.



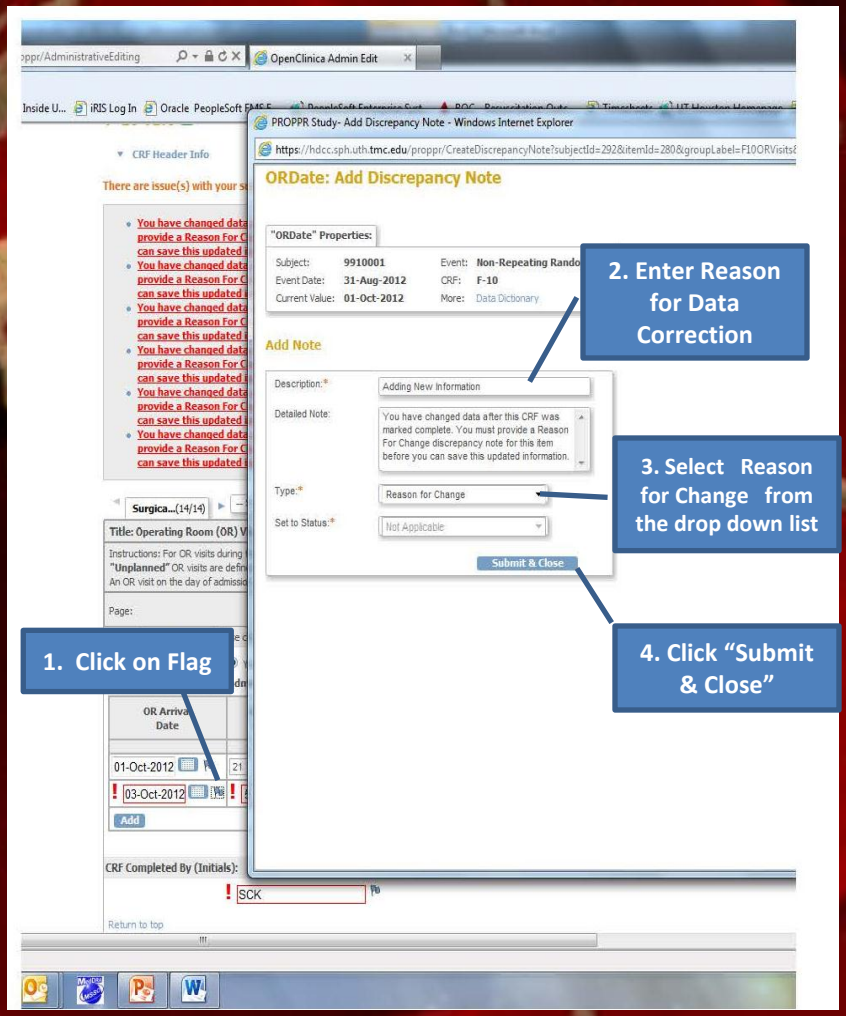
OpenClinica Tips: Correcting "Saved Complete" CRF's

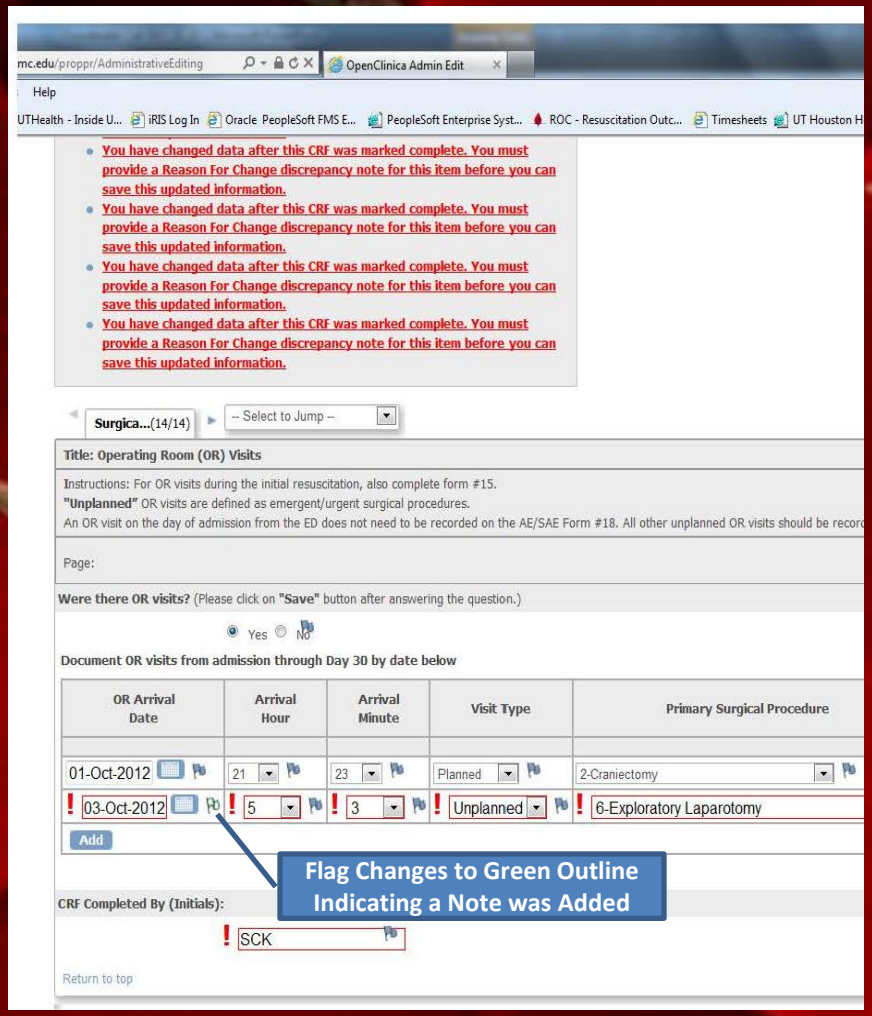
Click on the 'save' button once - OpenClinica will highlight which items need a reason for change discrepancy note.



OpenClinica Tips: Correcting "Saved Complete" CRF's

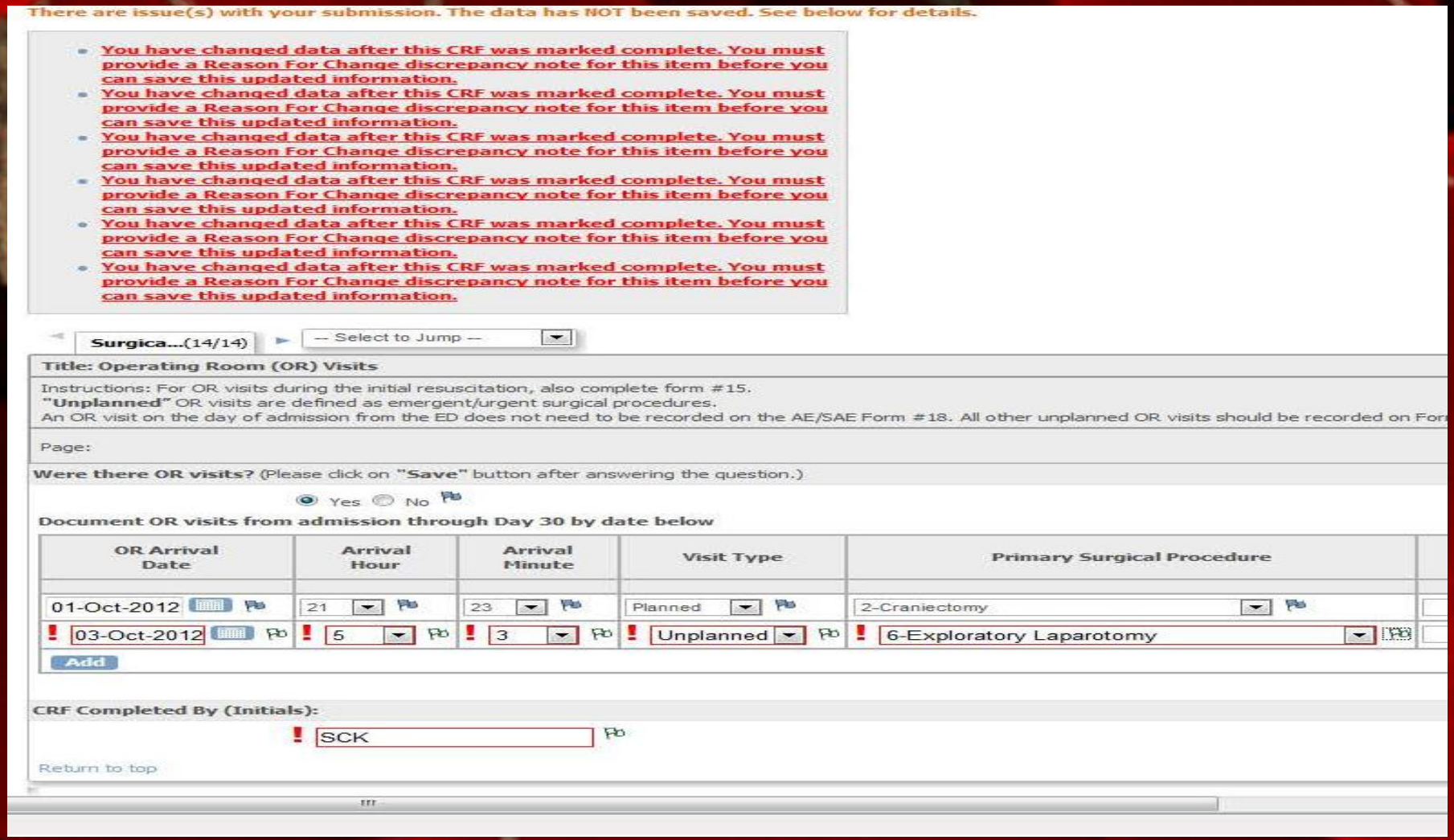
Click on the flag by each data field your correcting.
(Look for the red exclamation point.)

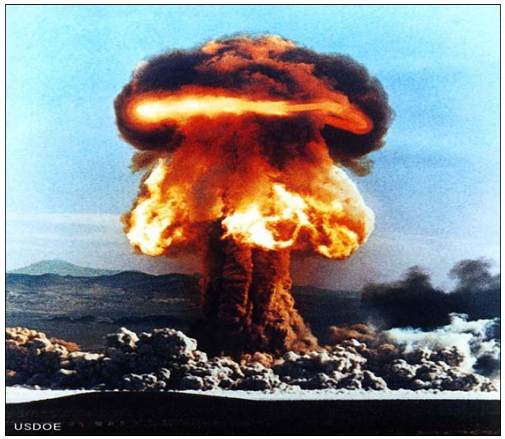




OpenClinica Tips: Correcting "Saved Complete" CRF's

Once a discrepancy note is created for each flag, click the "save" button on the bottom right.





Don’t open multiple instances of OpenClinica. One instance will quite likely time out and you will lose data.

On any e-CRF formatted as a table, record one line of data at a time before saving the record.

F-14 v1.0 **Subject id: 00880567** **Admission Date Sep 18, 2012**

CRF Header Info

Click the flag icon next to an input to enter/view discrepancy notes. Please note that you can only save the notes if CRF data entry has already started.

Exit

A Secti...(1/18) | B Secti...(0/20) | C Secti...(0/5) | -- Select to Jump --

Title: A Section - TEG Results

Instructions: The 2 hour and beyond TEG/Multiplate tests should only be performed on randomized subjects. If data value is unknown, use the codes below to indicate the reason.
NA = Not Applicable (eCRF Code –995) ND = Not Detectable (eCRF Code –996) NK = Unknown (eCRF Code –997)
NP = Not Palpable (eCRF Code –998) NR = Not Recorded/Not Done (eCRF Code –999)

Page: 1

Did subject die before any research blood samples could be obtained? (Please click on "**Save**" button after answering the question.)

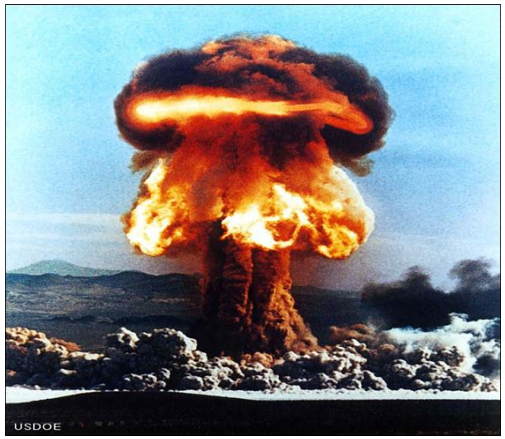
Yes No

TEG Results:

Sample Time Point	Test Done?	Date	Start Hour	Start Minute	Split Point (min.)	R-Time (min)	K-Time (min)	Alpha Angle (%)	Max. Amp. (mm)	G-Value (d/sc)	Ly30 (%)	Ly60 (%)	TMRTG	MRTG	TG	Lab Label	
1st Available																	X
2 hour																	X
4 hour																	X
6 hour																	X
12 hour																	X
24 hour																	X
48 hour																	X
72 hour																	X

Add

Don’t do this…..



On any e-CRF formatted as a table, don't skip lines.

F-11 Subject id: 00880567 Date: 2012-09-18 18:25:00.0

CRF Header Info

IR Visit (1/13) -- Select to Jump --

Title: Interventional Radiology (IR) Visits

Instructions: For IR visits during the initial resuscitation, also complete form #15.

Page: Mark Case Report Form (CRF) Complete Save Exit

Were there IR visits? (Please click on "Save" button after answering the question.)

Yes No

Document IR visits from admission through Day 30 by date below.

Arrival Date	Arrival Hour	Arrival Minute	Visit Type	Primary IR Procedure	Additiona IR Procedure	Additiona IR Procedure	Additiona IR Procedure	Additiona IR Proce
12-Feb-2013	1	18	Unplanned	13-Thoracoabdominal, Diagnostic	(select one)	(select one)	(select one)	(select one)
				(select one)	(select one)	(select one)	(select one)	(select one)
13-Feb-2013	19	12	Planned	8-Pelvic, Therapeutic				

Add

Don't do this…..

CRF Completed By (Initials):

Return to top

Chapter 18 – Research Laboratory

Section 18.1 Laboratory Manual of Procedures

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: TABLE OF CONTENTS FOR LAB MANUAL	Version # 2
SOP NUMBER:	Page 1 of

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: PROPPR One Sheet	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: To outline the basic flow of PROPPR research study.

SCOPE: Applies to the procedure for randomizing subjects and obtaining subject samples at each sample time point. These samples are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will obtain the subject blood samples.

Highest Acuity Trauma Patient arrives at ED:

1. **Study personnel will ensure that Patient is eligible/ineligible as outlined in PROPPR protocol by evaluating the ABC Score greater than or equal to 2 of the following:** **Penetrating injury=1**
   HR >120=1
   SBP≤90=1
   Positive FAST=1
2. **Patient must receive at least 1 unit of blood products (and no more than 3 units RBCs) in first hour from admission.**

3. **PROPPR/Massive Transfusion protocol must be activated within 2 hours of admission.**
   ********Attending Trauma Surgeon Gestalt can override a ABC score <2********

Initial Blood Draw:

******All non-excluded patients will get Initial blood draw******

1. **Five (5) tubes of blood are drawn by ED clinical nurse, for a total of 23 ml (in sequential order):**
   (R1) 2.7mL blue top
   (R2) 4.5mL blue top
   (R3) 4.5mL blue top
   (R4) 4.5mL blue top with benzamidine
   (R5) 5mL lavender/grey top Cyto-Chex BCT tube

2. **PROPPR study personnel drops off 3 (4.5ml) Blue top and 1 (5ml) Lavender Gray top tubes at Clinical Lab for processing, or coordinator processes samples per site specific protocol.** ***(If PROPPR randomized, (5ml) Lavender Gray top tube will be shipped as whole blood)***
3. **PROPPR study personnel runs TEG/Multiplate tests on remaining 2.7ml Blue top sample tube, only if a Screen Failure's ABC score was 2 or greater or patient is randomized into PROPPR, regardless of ABC score.**

If seal on the Blood Cooler is broken, the patient is randomized into PROPPR, and there will be 7 sequential blood sample draws

Time 2, 4,6,12,24,48,72 Sequential draws:

- **Study personnel have a +\- 30 minute window to get 2-72 hour blood samples.**
- **OR and IR: For OR:** Study personnel will be responsible for ensuring that all tubes are present so that the blood is collected at the appropriate time (+/- 30 minutes) and follows the same clinical process as Initial Blood Draw samples. **For ICU:** Once patient is in the ICU the study coordinator can set up "buckets" or "packets" for subsequent tubes.

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: EQUIPMENT REQUIRED	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: To outline the steps necessary to run the blood clot and platelet analysis testing on the TEG and Multiplate machines and to ensure the most accurate result is obtained.

SCOPE: Applies to the procedure for testing subject samples at each sample time point where sufficient blood is collected to run tests. These samples are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform TEG/Multiplate testing.

EQUIPMENT

- TEG Machine
- Multiplate Machine
- Small refrigerator with freezer (a small "college dorm room size" is sufficient)
- Tabletop centrifuge
- Protective equipment (gloves, eye protection)
- Chux for placement under the machines
- Pipettes
- Pipette tips (will need 3 sizes: 1mL and 50 μL and 20μL)
- Reagents for TEG and Multiplate machines
- Pins/Cups/test cells for TEG and Multiplate machines
- Small plastic container to dispose of contaminated pipette tips in-between test steps
- Biohazard bin

OTHER:

- The equipment used for sample collection and storage should be the same as outlined in this protocol.
- Any significant variations in equipment must be recorded and emailed to the Lab Committee.
- Details of all purchases of tubes should be recorded (e.g. lot/batch no. and expiration date).
- Calculate the quantities of disposable supplies and reagents needed based on your site's projected workload. Allow sufficient time for the delivery of the required supplies from the vendors.
- Local preferences, procedures and regulations may require a site to have access to items that are not on the list.
- The TEG and Multiplate machines must be kept in a location that allows for prompt testing after obtaining each sample.
- Each site center will receive PROPPR barcoded ID labels provided by the Data Coordinating Center. These labels will be placed on appropriate forms, blood collection tubes, and aliquot cryovials.

RESOURCES:

- TEG Manufacturer's Operation Manual
- Multiplate Manufacturer's Handbook

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SUPPLIES - ORDERING	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: Ordering the PROPPR supplies

SCOPE: Each site needs to have these supplies on hand and in a supply great enough to properly facilitate the processing of the blood samples.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will be interacting with supplies required for study.

Ordering TEG/MULTIPLATE Reagants:

It is the duty of the Project Coordinator to keep up to date on stocked Lab Supplies and Reagents, and make sure that they have been properly pre-mixed for tests (see **SOP: Mixing Reagents**). Your specific TEG/Multiplate Sales Support Representative should know what you need and be able to stock any regents that need re-supply.

Ordering the Yellow Collection Bucket for the Sequential Samples

Global Industrial Container- Model 550107YL- 5.5”x5”x13.5”
http://www.globalindustrial.com/p/storage/bins-totes-containers/stacking-bins/premium-stacking-bin-5-1-2-x-13-1-2-x-5-yellow

Ordering the Blood Collection Vacutainer Tubes:

- Citrate Blue Tubes- Kendall Monoject Vacutainer Blood Collection Tubes- (10.25 X 64 mm), Draw-2.7 ml, Stopper Coating - Silicone, Buffered Sodium Citrate 3.2% Solution, Cat No 8881340288 (or 22-340288)
- Citrate Blue Tubes- BD Vacutainer Blood Collection Tubes- (13 X 75 mm), Draw-4.5 ml, Stopper Coating - Silicone, Buffered Sodium Citrate 3.2% Solution, Cat No 369714
- Citrate Blue Tubes- BD Vacutainer Blood Collection Tubes- (13 X 75 mm), Draw-4.5 ml, Stopper Coating - Silicone, Buffered Sodium Citrate 3.2% Solution, Cat No 369714 WITH BENZAMIDINE (see instructions below)
- Cyto-Chex BCT tube 5 mL, Streck, Omaha, NE, Catalog No.213362 (www.streck.com)

Ordering the Benzamidine:
Contact the site-specific person that coordinates Chemical/Clinical Lab orders, Benzamidine is manufactured by Sigma, call number (Sigma #434760-25G)

Biohazard Sample Bags and Sharps Containers

Each site should have these as standard hospital supply, check with ED or clinical lab supplier

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SUPPLIES - ORDERING	Version # 1
SOP NUMBER:	Page 2 of

Shipping containers:

ThermoSafe® Diagnostic Specimen Mailing Systems (for Cyto-Chex BCT flow tubes)
http://www.thermosafe.com/
Model #470 (capacity 8 tubes) and/or Model #476 (capacity 3 tubes)

Tegrant® ThermoSafe® Insulated Shipper Multipurpose Containers
03-525 Series Shippers

[Shipping containers also available from http://www.fishersci.com/
19-075-384C]

Polar Packs

Freezer boxes

RESOURCES:

- PROPPR SOP Biospecimen packing and Shipping
- TEG and MULTIPLATE SUPPORT

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SUPPLIES REQUIRED	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: Documenting the needed supplies for obtaining and processing the lab samples.

SCOPE: Each site is to have the PROPPR specific supplies and materials needed to successfully gather clinical labs and process.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will be interacting with supplies required for study.

Equipment and Supplies

Sample Tubes

- Citrate Blue Tubes- Kendall Monoject Vacutainer Blood Collection Tubes- (10.25 X 64 mm), Draw-2.7 ml, Stopper Coating - Silicone, Buffered Sodium Citrate 3.2% Solution, Cat No 8881340288 (or 22-340288)
- Citrate Blue Tubes- BD Vacutainer Blood Collection Tubes- (13 X 75 mm), Draw-4.5 ml, Stopper Coating - Silicone, Buffered Sodium Citrate 3.2% Solution, Cat No 369714
- Citrate Blue Tubes- BD Vacutainer Blood Collection Tubes- (13 X 75 mm), Draw-4.5 ml, Stopper Coating - Silicone, Buffered Sodium Citrate 3.2% Solution, Cat No 369714 WITH BENZAMIDINE (see instructions in **SOP Mixing Reagents**)
- Cyto-Chex BCT tube 5 mL, EDTA+ preservative, Streck, Omaha, NE, Catalog No.213362 (www.streck.com)

Cryovials for Aliquoting

Houston DCC should provide all the necessary cryovials.

Yellow Collection Bucket for the Sequential Samples

Global Industrial Container- Model 550107YL- 5.5”x5”x13.5”
http://www.globalindustrial.com/p/storage/bins-totes-containers/stacking-bins/premium-stacking-bin-5-1-2-x-13-1-2-x-5-yellow

Biohazard Sample Bags and Sharps Containers

Site should have these as standard hospital supply

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SUPPLIES REQUIRED	Version # 1
SOP NUMBER:	Page 2 of

Shipping containers:

ThermoSafe® Diagnostic Specimen Mailing Systems (for Cyto-Chex BCT flow tubes)
http://www.thermosafe.com/
Model #470 (capacity 8 tubes) and/or Model #476 (capacity 3 tubes)

Tegrant® ThermoSafe® Insulated Shipper Multipurpose Containers
03-525 Series Shippers

[Shipping containers also available from http://www.fishersci.com/
19-075-384C]

Polar Packs

Freezer boxes

Refrigerator/Freezer

Wherever the TEG and Multiplate machines are located, there needs to be a refrigerator with freezer in the immediate area to store reagents and samples. Size and Type of the refrigerator will vary for each site, as required by the space allocated in site-specific lab. A small "college dorm" unit is fine.

- The equipment used for sample collection and storage should be the same as outlined in this protocol.
- Any significant variations in equipment must be recorded and emailed to the Lab Committee.
- Details of all purchases of tubes should be recorded by the Study Coordinator for reference (e.g. lot/batch no. and expiration date, Expiration logbook to be kept with reagent supplies in Lab).
- Calculate the quantities of disposable supplies and reagents needed based on your site's projected workload. Allow sufficient time for the delivery of the required supplies from the vendors.
- Local preferences, procedures and regulations may require a site to have access to items that are not on the list.
- The TEG and Multiplate machines must be kept in a location that allows for prompt testing after obtaining each sample.
- Shipping materials and instructions are outlined under **SOP: Biospecimen Packing and Shipping**.
- Each site center will be supplied with the cryovials used for sample aliquots and storage at -80°C
- Each site center will receive PROPPR barcoded ID labels provided by the Data Coordinating Center. These labels will be placed on appropriate forms, blood collection tubes, and aliquot cryovials.

RESOURCES:

- Houston Coordinating Site- PROPPR Manual of Operations

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: General Research Coordinator Lab Guidelines for TEG and MULTIPLATE testing	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: To outline the steps necessary to run testing for the PROPPR study to ensure that samples are run efficiently, correctly and safely.

SCOPE: Applies to the procedure for testing subject blood samples at each sample time point where sufficient blood is collected to run tests. These samples are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform testing.

SAFETY AND QUALITY CONTROL:

- Blood Borne Pathogens training must be completed prior to working with blood samples.
- Always follow universal and Blood Borne precautions.
- Gloves and Eye protection are to be worn at all times.
- QUALITY CONTROL MEASURES:
    - To be run once a week.
    - Level I and Level II Controls should be located in refrigerator.
    - Each has a pair of tubes: the lyophilized control solution and a tube full of diluent (or water)
    - Add the entire tube of water and shake vigorously
    - Let stand for 5 min; then shake vigorously again
    - Let stand another 5 min, and then proceed with running quality control tests.

GENERAL WORKFLOW OF RESEARCH LAB TESTS (when running TEG and MULTIPLATE):

- Keep samples in warmer (on Multiplate block) while preparing tests
- Take all needed reagents out of the fridge to warm to room temperature
- Check volumes and expiration dates, and thaw or open new reagents as needed
- Record any old results and clear all channels to be used
- Input patient and sample time into each computer
- Set up cups, pins, and test cells for each planned test
- Run tests in order of test priority list below
- Once tests start successfully, dispose of used pipet tips
- As tests are completed, print/record results and clear channels
- Dispose of used cups/pins/test cells and any leftover blood
- Check sharps, biohazard, and glass disposal
- Shred any leftover protected health information

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: General Research Coordinator Lab Guidelines for TEG and MULTIPLATE testing	Version # 1
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SPECIAL SCENARIO STRATEGIES

TEST PRIORITY LIST: If short on blood (NOT due to short tube, but need to redo a test, etc.)

1. **TEG (citrated kaolin)**
2. **MULTIPLATE (ADP, TRAP, ASPI, COL, and RISTOhigh)**

PROCEDURE FOR DISCARDING EXTRA BLOOD at the end of tests:

- Using the 1mL pipette (set to 1000), pipette bleach solution directly into the tube.
- Let sit for 30 minutes.
- Discard disinfected blood down the drain
- Replace the cap on the tube, and discard in the sharps bin.

PROCEDURE FOR DISCARDING WASTE (follow your site's policy):

- **Sharps container:**
  - ONLY for discarding blood-contaminated glass (e.g., used blood tubes)
  - DO NOT fill past the "Fill line"
  - When full, tape over top, write a note saying "Please discard" and place in a location per your site's policy
  - Assemble a new empty sharps container.

- **Red biohazard bin:**
  - For ANY NON-SHARP ITEM CONTAMINATED WITH BLOOD (Pipette tips, gloves, paper towels, cleaning materials, etc.)
    - Pipette tips NOT considered a sharp.
  - While running tests:
    - Place blood-contaminated pipette tips in the plastic beaker on the bench lined with specimen bag
    - When done with tests, discard entire baggie into red biohazard bin.
    - Line plastic beaker on bench with a new specimen bag.
  - If large biohazard bin is full:
    - Leave bag inside it, tie up the top
    - Write a note: "Please discard" and tape to top of bin
    - Place bin out for pickup
  - Get a new red biohazard bag and place it in the second biohazard bin for use
  - Only fill one biohazard bin at a time – rotate containers.

- **White cardboard glass bin:**
  - Only for glass bottles that are **not** contaminated with blood
    - (e.g. Multiplate bottles)

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SOP TITLE: General Research Coordinator Lab Guidelines for TEG and MULTIPLATE testing	Version # 1
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- **Regular trash bin:**
  - Everything else that is not contaminated.

- **Paper shredder**
  - For all items containing PHI.

CLEANING Checklist

- Replace chux on the bench as needed. Should be no visible stains.
- To clean surfaces: Use 10% bleach solution + kim wipes or paper towels.
- After preparing a solution: Rinse the beaker with deionized water.
- At the end of running tests, be sure to close the small plastic bag in the beaker, which temporarily holds biohazard materials on the bench between tests.
- Be sure all reagents and test materials have been stored accordingly.

REFERENCES

- PROPPR SOP's for Lab testing and PROPPR Protocol

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SPECIMEN COLLECTION: OBTAINING THE INITIAL AND SEQUENTIAL BLOOD SAMPLES	Version # 2
SOP NUMBER:	Page 1 of

PURPOSE: To outline the steps necessary to obtain the Initial Blood sample (the first blood sample taken in the ED) and to obtain the sequential blood samples (2, 4, 6, 12, 24, 48 and 72 hours after ED arrival).

SCOPE: Applies to the procedure for obtaining subject samples at each sample time point. These samples are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will obtain the subject blood samples.

OVERVIEW

Unless there is an initial obvious exclusion, initial blood samples will be drawn as soon as possible in the Emergency Department on all patients admitted under the highest level of trauma activation. All patients arriving to the ED with the highest level of trauma will be noted on the screening log. Those patients who become randomized subjects in PROPPR will have additional blood samples drawn at 7 sequential collection time points.

With the exception of TEG and Multiplate analyses, blood samples collected for this study will be processed as described, then shipped to Houston and analyzed at the Houston Core Laboratory. It is vitally important to collect specimens using standardized methods to insure the integrity of the specimens, the data and any conclusions generated. Each site is responsible for adhering to and processing all samples according to the procedures described in the **SOP: Specimen Processing**. Each site must have access to a minus 80°C freezer for the temporary storage of sample aliquots until the samples are shipped to the Houston Core lab. This will apply to both the initial draw sample on eligible screened first draw only patients and the initial and subsequent samples on randomized patients.

Samples to be obtained at each time point:

1 x 2.7ml Blue top citrated tube for functional assays (TEG and Multiplate)
2 x 4.5ml Blue top citrated tube for coagulation assays
1 x 4.5ml Blue top citrated tube with benzamidine
1 x 5ml Lavender/grey Cyto-Chex BCT with preservative for flow cytometry

Five (5) tubes of blood are drawn, for a total of 23 ml of blood for EVERY sample

Prepare the tubes, specimen requisition form (site specific), labels, etc. needed for the specimen collection process. The sequential order of draw should be:

(R1) 2.7mL blue top
(R2) 4.5mL blue top
(R3) 4.5mL blue top
(R4) 4.5mL blue top with benzamidine
(R5) 5mL lavender/grey top Cyto-Chex BCT tube

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SOP TITLE: SPECIMEN COLLECTION: OBTAINING THE INITIAL AND SEQUENTIAL BLOOD SAMPLES	Version # 2
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Tubes are to be numbered (R1, R2, R3, R4, and R5) to assist the clinical staff in prioritizing the collection of the samples. The lavender/grey Cyto-Chex BCT sample tubes contain a strong anticoagulant (EDTA). **It is important to make every effort to follow the correct order of draw to prevent contamination of samples.**

INITIAL BLOOD SAMPLES

Unless there is an initial obvious exclusion, initial blood samples will be drawn as soon as possible in the Emergency Department on all patients admitted under the highest level of trauma activation. If a patient is later found to be ineligible, the sample will be discarded.

- PROPPR study personnel responds to the Emergency Department for all of the highest level of trauma activation patients (unless the trauma pager contains information that the patient does not meet initial eligibility requirements (pregnant, CPR> 5 minutes, pediatric patient)
- Study personnel will verify that the patient is highest level of trauma activation, as outlined in the protocol. Initial study blood draws will not be obtained on obviously non-eligible patients. However, all screened patients will be noted on the Screening Log and given a Study ID number.
- All eligible screened patients will have the initial blood samples drawn as quickly as possible upon ED arrival. Do not wait to draw the initial labs. **It is important to attempt to obtain the labs before significant blood products or IV fluids have been administered.**
- Study personnel will give the qualified ED clinical staff the five (5) PROPPR blood vials.
- Blood sample collection will only be performed by qualified ED staff and every attempt will be made to coordinate blood draw with a clinical draw. Study personnel will be present and responsible for making contact with the ED staff in charge of the draw, reminding them that the blood draw is needed, and taking possession of drawn blood from the ED staff.
- Acceptable blood draws can be from peripheral, central, intraosseus, or arterial line. The study personnel will document where the sample was obtained. If necessary, ask the ED staff for help regarding the site where the sample was obtained.
- Form 1 will be filled out with data regarding initial lab draw

    - Form 13 will be filled out for each blood draw. Information regarding timing, volume, site and location of blood draw will be entered on Form 13.
    - **Ask the ED staff to completely fill all tubes**. All specimens collected with anticoagulants need to have enough volume to insure that there are no improper dilutional effects. An improper ratio of anticoagulant to whole blood may interfere with the measurements.
    - It is important to record the approximate blood volume for each blood vial. Any volume falling below the full volume must be documented in the blood collection forms.

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SPECIMEN COLLECTION: OBTAINING THE INITIAL AND SEQUENTIAL BLOOD SAMPLES	Version # 2
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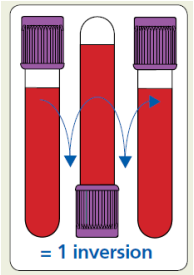
- Immediately after collection, it is imperative to **gently invert (in a back/forth motion)** all of the blood vials **10 times** to reach to mix the additive/anticoagulant and the blood sample (Figure) **Do NOT shake the vials**.
- Keep the blood sample at room temperature (18-22 °C) throughout processing.



<u>ONLY PATIENTS WITH AN ABC SCORE GREATER THAN OR EQUAL TO 2 WILL HAVE TEG AND MULTIPLATE PROCESSING COMPLETED</u>.

Note: <u>All enrolled patients</u> will have TEG/Multiplate processing regardless of ABC score.

Take vial #R1 to the TEG and Multiplate machine for processing by the research staff, if the patient's ABC score was ≥ 2**. (See SOP: TEG and Multiplate.)**

Take vials #R2-R5 to the clinical lab or equivalent site per local site protocol for processing. (See **SOP: Specimen Processing**) for instructions.

At the time of the initial blood draw, it may not be known whether a patient will be randomized into the study. Therefore, the initial blood sample tubes should be labeled per each site's requirements (i.e. addressograph, with Trauma name, MRN) or any other labeling required by the site's clinical lab in order to process the research laboratory samples.

Sometime between hour 0 and 2 hours, the patient will either be randomized into PROPPR or remain a screened eligible initial draw only patient.

<u>RANDOMIZED SUBJECTS (2, 4, 6, 12, 24, 48, and 72 hours after ED arrival)</u>
ONLY RANDOMIZED PATIENTS WILL HAVE SEQUENTIAL 2-72 hour sampling.

Using the time the trauma patient was admitted to the ED; calculate the times for the 2, 4, 6, 12, 24, 48, and 72 hour blood sample. It is ok to "round up" or "round down" on the time to the nearest 15 minute.

For example:
Patient admission time: 08:18
2 hour sample: 10:15

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4 hour sample: 12:15

Patient admission time: 08:23
2 hour sample: 10:30
4 hour sample: 12:30

Research Staff will need to know the physical location of the patient for each timed sample. The research staff may need to obtain the sample while the patient is in Interventional Radiology, the Operating Room, the ICU or the other locations.

Timing Window for 2-72 Hour Lab Draws

- All attempts will be made to obtain study samples at the designated time intervals. Timing is important.
- The clinical staff obtaining the samples (usually the ICU Nurses) have a +\- 30 minute window to get
  2-72 hour draws.
  - If the scheduled draw is to occur at 16:00, the nurse must get the draw no earlier than 15:30 and/or no later than 16:30. The purpose of this is to allow coordination with RN work flow, so as not to place undue burden on ICU staff or the patient.
- If any samples are missed, please obtain the draw at next time point. Document the missing draw and the reason the sample was not obtained on Form 13.
- Blood should be drawn from in-dwelling line (arterial, central or I.V.). If this is not possible, and venipuncture is required, please try to coordinate the sample with one of clinical need.
- Research staff should go to the subject's bedside 30 minutes before the time of the draw to remind the clinical staff of the need for the draw, to assist them with the draw, and to collect the blood vials.

Five (5) tubes of blood are drawn, for a total of 23 ml of blood for EVERY sample
Prepare the tubes, specimen requisition form (site specific), labels, etc. needed for the specimen collection process. The sequential order of draw should be:

(R1) 2.7mL blue top
(R2) 4.5mL blue top
(R3) 4.5mL blue top
(R4) 4.5mL blue top with benzamidine
(R5) 5mL lavender/grey top Cyto-Chex BCT tube

Tubes are to be numbered (R1-R5) to assist the clinical staff in prioritizing the collection of the samples.

The lavender/grey Cyto-Chex BCT sample tubes contain a strong anticoagulant (EDTA). **It is important to make every effort to follow the correct order of draw to prevent contamination of samples.**

- Form 13 will be filled out for each blood draw. Information regarding timing, volume, site and location of blood draw will be entered on Form 13.

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SPECIMEN COLLECTION: OBTAINING THE INITIAL AND SEQUENTIAL BLOOD SAMPLES	Version # 2
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- **Ask the clinical staff to completely fill all tubes**. All specimens collected with anticoagulants need to have enough volume to insure that there are no improper dilutional effects. An improper ratio of anticoagulant to whole blood may interfere with the measurements.
- It is important to record the approximate blood volume for each blood vial. Any volume falling below the full volume must be documented in the blood collection forms.
- Immediately after collection, it is imperative to **gently invert (in a back/forth motion)** all of the blood vials **10 times** to reach to mix the additive/anticoagulant and the blood sample. **Do NOT shake the vials**.
- Keep the blood sample at room temperature (18-22 °C) throughout processing.

Take vial #R1 to the TEG and Multiplate machine for processing by the research staff. (**See SOP: TEG and Multiplate.)**

Take vials #R2-R5 to the clinical lab or equivalent site per local site protocol for processing. (See **SOP: Specimen Processing)** for instructions.

SAMPLES IN THE OR

For subjects in the Operating Room at the time of a scheduled draw, the research staff will need to bring all of the PROPPR blood vials with them (5), labels, specimen bag, and requisition form for the clinical laboratory. Please ask the Anesthesiologists to obtain the samples.

SAMPLES IN THE ICU:

Once the patient is admitted to the ICU, the research staff can set up study "buckets" for the sequential samples.

ICU Bucket/Packet

Buckets for each randomized subject will be placed in the ICU room with the subject, in a location that is visible, but does not impede the work flow of the ICU medical staff.

To prepare a study bucket/packet you will need:

- 5 PROPPR tubes for each timed draw, *(4 Citrated Blue tubes[3 regular, 1 with Benzamidine solution], 1 BCT tube)*
- Specimen bags (2 bags for each timed draw – 1 for the clinical lab samples and 1 for the TEG/Multiplate samples and BCT tube for shipping)
- Clinical lab requisition forms (You need a lab form for each time draw)
- Labels for each tube. See (**SOP: Labeling the Sequential Samples)** for details.
- 1 physician order form (standing orders for the study, pre-signed by the PI)
- 1 bucket/packet instruction form

- Complete the physician order form and bucket instruction form with the dates and times of all of the sequential draws.
- Tape the bucket/packet instruction form to the bucket and check that all draws are documented

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- Talk with the subject's bedside nurse about the study. Explain the study if necessary. Place the study bucket/packet in the subject's room. Give the bedside nurse the Physicians Order sheet and discuss the need for the timed draws. Thank them for their help.

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ICU Bucket Instruction Form
Half Sheet to be attached bucket, for tracking of blood draws:

PROPPR Study: DR. _____
Please collect 5 tubes (4 Citrated Blue tubes, 1 Lavender/grey BCT tube).
Only use the PROPPR study vials.

2HR Sample Date:_____ Time:_____
4HR Sample Date:_____ Time:_____
6HR Sample Date:_____ Time:_____
12HR Sample Date:_____ Time:_____
24HR Sample Date:_____ Time:_____
48HR Sample Date:_____ Time:_____
72HR Sample Date:_____ Time:_____

Please Date and Time the Requisition Form

Thank you for your help! For questions/concerns please contact:
Research Coordinator Contact Info/ PI Contact Info

Physician Order Form (standing orders)

Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR)
CHR Approval #:

Please draw 5 tubes (4 Citrated Blue tubes, 1 lavender/grey BCT tube) at the following dates/times:
Only use the PROPPR study vials.

2HR Date/Time:
4HR Date/Time:
6HR Date/Time:
12HR Date/Time:
24HR Date/Time:
48HR (Day 2) Date/Time:
72HR (Day 3) Date/Time:

SITE PI SIGNATURE HERE:

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RESOURCES:

- PROPPR Protocol
- PROPPR Manual of Operations

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SOP TITLE: LABELING THE INITIAL SAMPLE	Version # 1
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PURPOSE: To outline the steps necessary for initial blood samples to be labeled correctly for the PROPPR study.

SCOPE: Applies to the procedure for labeling subject initial blood samples.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform testing.

SUPPLIES:
Each site will receive three batches of labels:

- **Initial Draw Only/Eligible, Screen Failure** (100 sets)
  - Two kinds of labels; special freezer safe labels for the tubes and labels for use on paper forms where indicated.
- **Randomized PROPPR Patient** (50 sets)
  - Two kinds of labels; special freezer safe labels for the tubes and labels for use on paper forms where indicated.
- Bright colored generic temporary PROPPR labels that can be placed on initial tubes indicating these are PROPPR patients and the order in which tubes should be filled. These labels have no ID numbers.

All Samples:

All sample tubes will begin processing with local site-specific labels (MR#, Trauma name, date and time) and a generic temporary PROPPR labels numbered 1 to 5 to designate order of blood draw and given to Clinical Lab for processing and aliquoting

Once study disposition of patient is known, Coordinator will affix the correct labels to initial draw tubes (and sequential draw tubes if applicable).

Scenario #1.
PROPPR Randomized Subject

Patient is Randomized:

- Coordinator runs TEG and Multiplate test on 2.7mL tube
- Coordinator affixes **PROPPR randomized paper** patient labels to CRF Form 1 and PROPPR patient freezer labels to all initial draw tubes and aliquots
- Assure that Study ID numbers are visible, date and initial.
- Corresponding PROPPR randomized patient freezer labels affixed **after** each draw has been **processed and aliquoted** by Clinical Lab. Corresponding subsequent draw paper labels attached to CRF Form 13.
- Whole blood BCT tube labeled and shipped **within 24 hours** to Houston

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Scenario #2.
Screen Failure and ABC score is 2 or greater
Patient is Initial Draw Only and Patient is eligible for TEG and Multiplate:

- Coordinator runs TEG and Multiplate test on 2.7mL tube
- After patient deemed **PROPPR initial draw only**, affix corresponding paper ID labels to CRF and freezer ID labels to all initial draw tubes and aliquots
- Assure that Study ID numbers are visible, date and initial.
- Samples frozen and batch shipped to Houston monthly

Scenario #3.
Screen Failture and ABC score is less than 2.
Patient is Initial Draw Only and Patient is not eligible for TEG and Multiplate:

- **NO TEG/Multiplate**, but should have plasma and whole blood BCT tube processed and aliquoted.
- Affix **PROPPR initial draw only** and corresponding paper labels to CRF Form 1 and freezer labels to all initial draw tubes and aliquots
- Assure that Study ID numbers are visible, date and initial.
- Samples frozen and batch shipped to Houston monthly

RESOURCES:

- PROPPR MOO and Protocol

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: LABELING THE SEQUENTIAL SAMPLES	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: To outline the steps necessary for sequential blood samples to be labeled correctly for the PROPPR study.

SCOPE: Applies to the procedure for labeling subject sequential blood samples.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform testing.

SUPPLIES:
Randomized PROPPR Patient sequential draw labels (2, 4, 6, 12, 24, 48, 72 hrs.)

All Samples:

All sample tubes will begin with local site-specific labels (MR#, Trauma name, date and time) and given to Clinical Lab for processing and aliquoting

After processing and aliquoting, Coordinator will affix the correct PROPPR sequential draw labels to samples. Subsequent draw labels with laboratory ID# will be attached to CRF Form 13.

PROPPR Randomized Subject

Patient is Randomized, and has 7 follow up blood draws in ED, IR, OR, ICU:

- Coordinator runs TEG and Multiplate test on 2.7mL tube
- Coordinator affixes **PROPPR randomized** patient paper labels to CRF Form 13 and freezer labels to sequential draw tubes and aliquots
- Assure that study ID and Randomization ID numbers are visible, date and initial.
- Corresponding draw PROPPR randomized patient labels affixed **after** each draw has been **processed and aliquoted** by Clinical Lab.
- Whole blood BCT tube labeled and shipped **within 24 hours** to Houston

RESOURCES:

- PROPPR MOO and Protocol

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: SPECIMEN PROCESSING	Version # 2
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PURPOSE: To outline the steps necessary to process the Initial Blood sample (the first blood sample taken in the ED) and to process the sequential blood samples (2, 4, 6, 12, 24, 48 and 72 hours after ED arrival).

SCOPE: Applies to the procedure for obtaining subject samples at each sample time point. These samples are run for **research purposes ONLY. The results are never used for clinical purposes**. Processing the TEG/Multiplate samples quickly and correctly is tantamount to the success of this study.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will obtain the subject blood samples.

SAMPLE PROCESSING

Requirements

- The sample should be processed as soon as possible and no later than **30 minutes after** the blood draw.
- The time elapsed between obtaining the blood and sample processing must be recorded on Form 13 for each sample.
- Please use **Table 1** and **Figure 1 and 2 (Appendix)** as a reference for the distribution of aliquots for specific tubes.

Processing the Initial Blood Draw tubes:

(1) Blue top tube 2.7 mL for functional assays (TEG and Multiplate) COMPLETED BY THE RESEARCH STAFF

- Process immediately per protocols for TEG and Multiplate (see **SOP TEG and Multiplate**)
- Maintain samples at room temperature (18-22 °C) throughout processing.

NOTE: All randomized patients will have TEG and Multiplate processed. For screen failures, only patients with an ABC score greater than or equal to 2 will have the Initial Blood Draw TEG and Multiplate processed/run.

NOTE: TEG/Multiplate should not wait for PROPPR randomization determination (completion of FORM 1). All TEG/Multiplate samples should be processed immediately upon ABC score greater than or equal to 2. If a patient has an ABC score less than 2 but the attending gestalt is yes, the patient is a randomized subject and TEG/Multiplate samples should be processed.

NOTE: Screen failure patients with ABC score less than 2 should not have TEG/Multiplate processed but should have plasma and whole blood BCT tube processed as described below.

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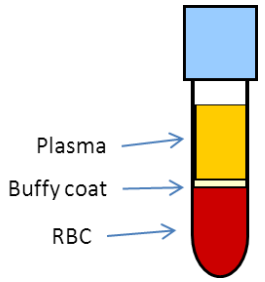
(2) 2 blue top tubes (4.5ml) and 1 blue top tube with benzamidine (4.5mL) (COMPLETED BY THE CLINICAL LAB or equivalent or per local site protocol):

- Maintain sample at room temperature (18-22 °C) throughout processing.
- Centrifuge the sample at **2500xg for 20 min**, at room temperature. This causes separation of the sample into 3 distinct phases: the upper layer is the platelet-free plasma (contains clotting factors), the narrow middle layer is the 'buffy coat' (white blood cells), and the bottom layer is the red blood cells (Figure).



- **NOTE: Use only centrifuge with swing bucket rotor.** If you have to convert maximum relative centrifugal force (RCF) to RPM: Determine centrifuge 's radius of rotation (in mm) by measuring distance from center of centrifuge spindle to bottom of device when inserted into rotor. Lay a ruler or draw a line from radius value in right-hand column value that corresponds to the device 's maximum rated g-force. Then read the maximum value from column at left (see **Appendix:** Nomogram for converting maximum relative centrifugal force (RCF, i.e., g-force) to RPM)
- Following centrifugation, the plasma should be aliquoted into the appropriate cryovials and immediately frozen at -80°C and stored at the site until shipped to the Core Lab in Houston (monthly, see **SOP Biospecimen Packing and Shipping**).
- While the tubes are being centrifuged, label the appropriate aliquot cryovials (see table) (**3 cryovials per patient per time point for randomized patients, or 4 cryovials for screen failure/initial blood draw only**) with the ID labels associated with the parent tubes and place the cryovials in a rack.

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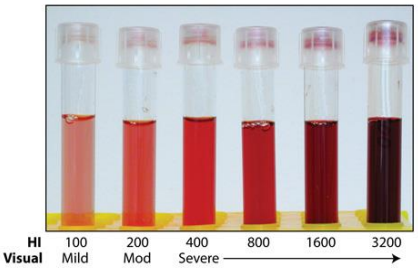
- After the centrifuge has stopped, remove and inspect the specimens for hemolysis. If the plasma is either red tinged or pink, the blood sample is hemolyzed. **Document the level of hemolysis in the Blood Collection form.** Grade the hemolysis from Slight Hemolysis, Moderate Hemolysis to Marked Hemolysis (Figure, the hemolysis grading chart). **Do not discard the sample**.

Hemolysis Figure.



- **Aliquot plasma from each of the 3 tubes (R2, R3, and R4) into a 3 ml screw-cap color coded cryovials**, as instructed below and the table (See Appendix) **(total 3 cryovials, per patient per time point for randomized patients, total 4 cryovials for Screen Failure/Initial Blood Draw Only).**

- *Note: When removing plasma after centrifugation do not disturb the white blood cells layer, called the buffy coat, which forms a thin layer between the upper plasma layer and the lower layer of packed red blood cells. It is critical that only the clear plasma be aspirated when preparing these sample aliquots.* ***Remove only 3/4 of the plasma volume above the buffy coat, and leave the rest (1/4) in the tube.***

Aliquot Example:

Transfer ~3/4 of the plasma volumes from the research tubes R2, R3 and R4 into the corresponding plasma cryovials (blue cap R2CP and R3CP and orange cap R4BP). Change transfer pipettes between tubes.

R2CP (Blue top cryovial) (R2 Citrate Plasma)
R3CP (Blue top cryovial) (R3 Citrate Plasma)
R4BP (Orange top cryovial) (R4 Benzamidine Plasma)

- After creating the aliquots, place the cryovials in the upright position into appropriate freezer boxes and store them at -80°degrees C until shipped to Houston Core lab.

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Note: **Please make sure that all cryovials have a study label (-80°C compliant) on them. Make sure the label is securely attached to the cryotube. Fasten the caps onto these vials**.
Specimens must be placed in the -80° degree C freezer in the upright position (freezer box with dividers) as soon as possible but no later than 60 minutes from the collection time. Record the date and time of freezing samples on the form *(PROPPR Biospecimen Collection Form).*

(3) Cyto-Chex BCT Lavender/grey top tube (R5) (COMPLETED BY THE RESEARCH STAFF):

Immediately after collection, gently invert the tube 10 times. Leave it at room temperature until ready to ship to UT Houston Core Lab. The Cyto-Chex BCT tubes must be shipped within 24h via overnight courier (see the **SOP Biospecimen Packing and Shipping**) to the UT Houston Core Laboratory.

NOTE: If a participant's blood draw yields less than the required number of tubes, collected samples still need to be processed and sent to the Houston Core Lab.

NOTE: Screen Failure/Initial Draw Only patients should have CytoChex BCT tube aliquoted and frozen without centrifugation. Screen Failure/Initial Draw Only patients will not have daily shipping of Cyto-Chex BCT tubes but frozen cryovials will be batch shipped with frozen plasma (see the instructions below)

INITIAL BLOOD DRAW: Cyto-Chex BCT Lavender/grey top tube *for* Screen Failure/Initial Draw Only Subjects

- Gently mix/re-suspend the blood by inverting the tube 10 times. **DO NOT SHAKE.**
- Label 1 purple top cryovial (see table, appendix) with the Lab Sample ID labels associated with the parent tubes and place the vials in a rack.
- Transfer the blood to pre-labeled purple top cryovials using the graduated transfer pipet:
    - R5WB blood (Purple top cryovial)

NOTE: It is recommended to keep specimen at room temperature until patient's eligibility for enrollment has been determined.

After creating the aliquots, place the cryovials in the upright position into appropriate boxes and store them at -80°C until shipping to Houston Central lab.

Note: **Please make sure that all cryovials have a study label (-80°C compliant) on them. Make sure the label is securely attached to the cryotube. Fasten the caps onto these vials**.
Specimens must be placed in the -80° degree C freezer in the upright position (freezer box with dividers)as soon as possible but no later than 60 minutes from the collection time. Record the date and time of freezing samples on the form *(PROPPR Biospecimen Collection Form).*

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NOTE: With the exception of TEG and Multiplate analyses, blood samples collected for this study will be processed as described, then shipped to Houston and analyzed at the Houston Core Laboratory. It is vitally important to collect specimens using standardized methods to insure the integrity of the specimens, the data and any conclusions generated.

Each site is responsible for adhering to and processing all samples according to the procedures described in this manual. Each site must have access to a minus 80°C freezer for the temporary storage of sample aliquots until the samples are shipped to the Houston Core lab. This will apply to both the initial draw sample on eligible screened first draw only patients and the initial and subsequent samples on randomized patients.

RESOURCES:

- PROPPR Lab Manual of Operations

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: TEG Testing	Version # 1
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PURPOSE: To outline the steps necessary to run the blood clot analysis testing on the TEG machine and to ensure the most accurate result is obtained.

SCOPE: Applies to the procedure for testing subject samples at each sample time point where sufficient blood is collected to run tests. These samples are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform TEG testing.

LOCATION OF TEG MACHINE: The TEG machine should be conveniently located near the ED, OR and ICU to allow the Research Staff to run the samples in an expedited manner. In addition, the reagents must be kept in a refrigerator located near the TEG machine.

MATERIALS, REAGENTS AND EQUIPMENT:

- TEG Machine
- Tabletop centrifuge
- Refrigerator/freezer
- TEG Kaolin reagent (purple label, located in your refrigerator)
- Pins/Cups (as one unit)
- Pipette tips (will need 2 sizes, 1mL and 20uL)
- Small plastic container to dispose of contaminated pipette tips in-between test steps
- Protective equipment (gloves, eye protection)

OVERVIEW:

1. Take all needed reagents out of the fridge to warm to room temp
2. Check volumes and expiration dates, and thaw or open new reagents as needed
3. Record any old results and clear all channels to be used
4. Input patient and sample time into each computer
5. Set up cups, pins, and test cells for each planned test
6. Run tests in order of test priority list below
7. Once tests start successfully, dispose of used pipet tips
8. As tests are completed, print/record results and clear channels
9. Dispose of used cups/pins/test cells and any leftover blood
10. Check sharps, biohazard, and glass disposal
11. Shred any leftover protected health information

TEST PRIORITY LIST:

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SOP TITLE: TEG Testing	Version # 1
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For full tubes, there should be enough blood to run all tests. Under-filled tubes have too high a citrate-to-blood ratio, and will give abnormal results on most of our functional tests. If a tube is less than ¾ full, this should be noted on the lab draw form.

However, if you're short on blood or have to redo a test, here is the test-by-test order of priority:

1. **TEG (citrated kaolin)**
2. **MULTIPLATE (ADP, TRAP, ASPI, COL, and RISTOhigh)**

SPECIAL NOTES:

- COMPUTER SYSTEM Log-in Information:
  - Startup computer
    - Login to computer system:
      - Username: TEG
      - Domain: XXXXX
      - Password: XXXX
  - Click on TEG V4 Icon on desktop:
      - User name: XXXXXXXXXXXX
      - Password: XXX
    - Once TEG Program starts, will ask for a user:
      - User: XXXXX
      - Password: There is no password. Simply hit 'enter'.
  - **If a pop-up occurs on the computer screen while in the TEG program to 'run a QC test' – hit skip.**
- REAGENTS:
  - Reagents located in labeled boxes in the refrigerator.
- PIPETS / PIPETTE TIPS
  - Standard laboratory handheld pipets and pipet-specific tips are used. The electronic pipettor associated with the Multiplate machine will not fit most standard laboratory pipets.
- CUPS/PINS
  - Located next to the machine.
  - Pins are held within the small plastic cup. Do not touch the pin. Only hold by the outside of the cup when handling.

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SOP TITLE: TEG Testing	Version # 1
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PROCEDURES:

PRE-TEST REAGENT PREPARATION

Kaolin

- Remove from refrigerator just before use.
- Spin down in small tabletop centrifuge for a few seconds before use.

$CaCl_2$

- Found in the Level I/II Control boxes in the refrigerator
- Store in the refrigerator if unopened; store at room temperature once opened
- If out: ORDER FROM HAEMONETICS

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TEST PREPARATION

Supplies, Machine and Subject ID/ Test ID Entry

- Reagents must be kept in the refrigerator.
- Check the bubble level on top of the TEG machine:
  - If the bubble is not in the center of the bullseye, the machine is not level; rotate the adjustable legs on either side of the bottom front of machine to straighten until bubble is in center of target
- If a pop up comes up asking to run a QC test – hit skip (QC test should be run per the Quality Control for TEG SOP).
- To run a test, click the 'TEG' icon located in upper right side of the toolbar.
- The screen will show the 4 channels with drop-down menus for test, patient ID, and sample ID for each channel (you will usually use channel 1, but if running multiple tests simultaneously any channel can be selected)
  - Test Name: Go to the drop down menu on the left that shows " ---N- Test"
    - 1st channel: select "CK – citrated kaolin TEG"
  - Patient ID:
    - To select subject ID number and hour, go to top drop down box on top right;
    - Existing patient: select from the drop-down menu;
    - New Patient: simply being typing in '#' (ex: [1507]) or scan barcode
    - If New Patient, answer "Yes" to pop-up "Is this a new patient?";
      - Enter Trauma Name for "Patient ID" (ex. [tr. Oscar]). Then hit done.
- In the bottom right box of channel fields, select hour of draw from drop-down menu (ex: [0h]).

Cup/Pin Set-up (IMPORTANT as this is the cause of many issues with tests)

- The cup/pin lever should already be in the load position
  - This is the way the machine should be left after a test.
- Slide white platform down until you hear a click, but **NOT** all the way down to the base of the machine.
  - If pushed all the way down, it will prevent the cup from loading properly.
- Place cup/ pin into the platform slot.
- While HOLDING ONTO the top of machine so it doesn't knock over (easy to do), slide the white platform with cup/pin up into black loading cylinder on machine.
- Once the platform is all the way up, press the white button on the base of the platform 3 TIMES to secure the pin.
- Once pin is in place, pull the platform back down about halfway, and NOT all the way to the bottom.
- Hold the bottom of platform with two fingers, and push down on the rim of the cup with your thumbs to securely seat the cup.
  - Don't push platform all the way down or you won't be able to properly seat the cup.

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SOP TITLE: TEG Testing	Version # 1
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SPECIFIC TEST PROTOCOL

Kaolin Test

- To start Kaolin test, click on the patient study ID for the next channel to highlight and activate the channel.
- Take Kaolin tube out of fridge and spin for a few seconds in tabletop centrifuge
- Set 20uL pipette to 20uL and pipette 20uL of CaCl2 (red top) into cup
- Prior to the next step, confirm that the correct channel is highlighted as active on the computer screen, and leave the mouse arrow hovering over the green "start" arrow so that you can start the test immediately after the next step without having to move the mouse again.
    - If unsure, click within one of the channel fields where the subject data is entered. This will activate this channel as the primary channel for the current test.
- Gently invert the blue-top tube of blood 5 times to ensure that the sample is well-mixed.
- Set 1000uL pipette to 1mL and gently pipette 1mL of blood into Kaolin vial (purple top).
- Tightly recap the blood-containing Kaolin tube, and mix 5 times by **gently** inverting purple tube.
    - DO NOT mix by pipette.
- Set 1000uL pipette to 340uL.
- Pipette 340uL of Kaolin + blood mixture (purple top) into the cup.
    - Place the tip of the pipet directly into the 20uL drop of calcium solution already in the cup, and pipet gently to avoid bubbles.
    - **DO NOT mix by pipetting**; extra mixing with Kaolin will cause unwanted contact activation.
- Slide the cup up and into position.
- Move the silver lever over to "test" position
- Hit start by clicking on the green icon at top of screen
- Watch the tracing for the first 10 minutes to ensure that the test is running correctly.
- Test will run for about 1 ½ hrs
- Once tests are finished, go to tracing review screen by clicking on "Done" from TEG channel setup screen; to view each tracing, double-click it; to return to tracing review screen, double-click the tracing.
- While in full-screen tracing view mode, click "Print" in upper left
- Sign and date the printout; make any notes on hardcopy; enter data into PROPPR clinical database
- To eject cup/pin move silver lever to "load" position. Push lever down and this will eject the cup & pin together. Push the white platform all the way down *past* the first click to the base of the machine; this will push up on the bottom of the cup to eject it.
- Put used cups/pins/pipette tips in biohazard waste bin
- Leave platform up and lever in load position when TEG not in use

DURING THE TEST

- To view test progress:
    - From TEG screen, click 'Done'
    - This will take you to the tracing review menu.
    - To return to regular TEG screen, click the TEG button at top of screen again.

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AFTER THE TEST

- Once tests are complete, go to tracing review screen by clicking on 'Done' from TEG channel setup screen;
- To view individual tracing, double-click it.
    - To return to tracing review screen, double-click the tracing
- While in full-screen tracing view mode, click "Print" in upper left corner.
- Print results; write your initials on the hardcopy and make notes as needed.
- Enter results into PROPPR online database, Openclinica
    - See **SOP- Lab Data Entry Procedures for data entry protocol**
- File the hardcopy accordingly in Research Record Binder

CLEANUP AFTER TESTS COMPLETED

- To eject cup/pin:
    - Move silver lever to "load" position.
    - Push lever down to eject the cup & pin together.
    - Push the white platform all the way down past the first click to the base of the machine; this will eject the cup.
- Discard used cups/pins/pipette tips in the biohazard waste bin.
- Leave platform up and lever in load position when TEG not in use

RESOURCES:

- TEG Manufacturer's Operation Manual

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SOP TITLE: Multiplate Testing	Version # 2
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PURPOSE: To outline the steps necessary to run the platelet function analysis on the Multiplate machine and to ensure the most accurate result is obtained.

SCOPE: Applies to the procedure for testing subject samples at each sample time point where sufficient blood is collected to run tests. These samples are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform Multiplate testing.

LOCATION OF MULTIPLATE MACHINE: The Multiplate machine should be conveniently located near the ED, OR and ICU to allow the Research Staff to run the samples in an expedited manner. In addition, the reagents must be kept in a refrigerator located near the Multiplate machine.

MATERIALS, REAGENTS AND EQUIPMENT:

- Specific to MULTIPLATE

OVERVIEW:

1. Take all needed reagents out of the fridge to warm to room temp. Keep samples in warmer while preparing tests.
2. Check volumes and expiration dates, and thaw or open new reagents as needed
3. Record any old results and clear all channels to be used
4. Input patient and sample time into each computer
5. Set up sensor cables and test cells for each planned test
6. Run tests in order of test priority list below
7. Once tests start successfully, dispose of used pipet tips
8. As tests are completed, print/record results and clear channels
9. Dispose of used /test cells and any leftover blood
10. Check sharps, biohazard, and glass disposal
11. Shred any leftover protected health information

TEST PRIORITY LIST:

For full tubes, there should be enough blood to run all tests. Under-filled tubes have too high a citrate-to-blood ratio, and will give abnormal results on most of our functional tests. If a tube is less than ¾ full, this should be noted on the lab draw form.

However, if you're short on blood or have to redo a test, here is the test-by-test order of priority:

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1. **TEG (citrated kaolin)**
2. **MULTIPLATE (ADP, TRAP, ASPI, COL, and RISTO high)**

SPECIAL NOTES:

- COMPUTER SYSTEM Log-in Information:
  - Username: multiplate
  - Password: XXXX
- REAGENTS:
  - Lyophilized reagents located in refrigerator.
  - Reconstituted reagents located in freezer.
  - Once an aliquot of reagent is thawed for use, store in refrigerator in special tray. Discard if expires before it is used up (See **SOP: Reagent Expiration Table**).
- PIPETTE TIPS
  - Located in clear box with orange insert next to machine. These are specific to the electronic pipettor; tips for standard handheld pipettors will not fit.
- TEST CELLS
  - Located on shelf next to machine.
  - Each tray contains 5 test cells.
  - Once a plastic tray of test cells is opened, the cells need to be used within 24hrs.

PROCEDURES

PRE-TEST REAGENT PREPARATION

- **CaCl2 solution:** (3mM CaCl2 in NaCl)
  - Ordered from Diapharma.
  - Storage: Unopened tubes stored in the refrigerator; once opened, the solution tube can be left on the Multiplate block in the holder. Be sure to tightly reseal to avoid evaporative loss.
- **Saline solution:**
  - A standard clinical/laboratory reagent; 0.9% sodium chloride solution ("normal saline"). Taken from clinical IV or stock bottles, common laboratory stock, or purchased from any standard laboratory supply company.
  - Stored on the Multiplate block in 3 or 5 mL standard laboratory round-bottomed polystyrene – be sure this will fit into the warmer block. Tightly reseal after each use to avoid evaporative loss.
  - To restock: Refill from any bottle or IV solution. MUST BE PRESERVATIVE-FREE.
- **ADP, TRAP, ASPI, and RISTO reagents:**
  - Refrigerator contains the thawed tray of reagent aliquots and the supply of lyophilized reagents to be reconstituted as needed.
  - Check expiration date/time on thawed, aliquoted reagents in the fridge. If expired, toss and thaw a new one.
  - The freezer contains all aliquots of reconstituted reagent.

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- If less than 3 aliquots left in the freezer supply for a particular reagent, reconstitute a new bottle of lyophilized reagent from the refrigerator.
  - Re-suspend the lyophilized reagent in 1mL reagent-grade, ultra-pure water at room temperature and mix gently by pipetting
  - Prepare 1.5mL tube aliquots of each reagent. If reconstituted and kept in a refrigerator, ADP, TRAP, RISTO ASPI reagents are stable for 7 days, except ASPI, which is only stable for 24 hours. If reconstituted, frozen and then thawed, ADP, TRAP, RISTO ASPI reagents are stable for 24 hours **(see SOP Reagent Expiration Table):**
    - For ADP / TRAP reagents: **200uL** (10 tests) per aliquot
    - For RISTO reagent: **500uL** (10 tests) per aliquot
    - For ASPI reagent: **42uL** (2 tests) per aliquot
  - Label the top of each aliquot with the name of the reagent.
  - Write your initials and date of reagent preparation on the top of the original reagent bottle.
  - Place aliquots in freezer box in a row behind the labeled reagent bottle.
- Once an aliquot is thawed for use, write the date of expiration on the top of the aliquot.
- **Frozen reagents take ~10min to thaw – BE SURE to check the amount of thawed reagent in the fridge before starting a test.**

- **COL reagent:**
  - Lyophilized powder is reconstituted at room temperature in 1.0mL of reagent-grade, ultra-pure water and stored in the refrigerator for up to 7 days – DO NOT FREEZE ONCE RECONSTITUTED.
  - Be sure to use a new pipet tip every time and pipet directly out of the glass bottle; since this won't be frozen and thawed, there is no need to aliquot.
  - The expiration date is written on the top of the bottle.
  - When expired, toss and reconstitute from the fridge.

TEST PREPARATION

- Remove MP reagent tray from refrigerator and place on the Multiplate test platform
- Check reagent expiration dates, and equilibrate to room temperature for 10 minutes before use.
- Click "F1 auto pipette" button
- Enter patient ID/sample ID together.
  - Example: [A-1460 Tr. Mike 12h] or scan barcode?
- Click "All tests" – will copy pt ID/sample ID into all channels.
- Select the following tests – ALL **CITRATED BLOOD** –
  - Run in the exact order shown to facilitate easier data entry:
    - ADP Test (citrated blood)
    - TRAPtest (citrated blood)
    - ASPI test (citrated blood)
    - COL test (citrated blood)
    - RISTO high (citrated blood)

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- Click "Start autopipette" button
- Put new test cells into all slots.
- Plug sensor cable into each channel. **THIS IS VERY IMPORTANT AND A COMMON THING TO FORGET.**
- Confirm the presence of small stir bars at the bottom of each test cell.
    - If no stir bar, discard test cell and replace with a new one.
    - If need to open new package, document date the package will expire on top of package.
- Follow the steps shown on the computer screen:
    - GO SLOW
    - DO NOT get ahead of the automatic pipette
    - Be sure to use the appropriate diluent (saline vs. saline-CaCl2); the electronic pipettor instructions will specifically detail which is to be used for each step
    - Be sure to mix the blue-top tube of blood by **gently** inverting 3 times prior to adding blood to the test cells to ensure that the sample is well-mixed.
- Special case to be aware of:
    - Occasionally the pipettor malfunctions and aspirates too large a volume of reagent, producing extensive bubbles. Watch the pipettor carefully at each step; if this happens, simply click "Step back" and re-do that step.
- Do not mix by pipette, as the magnetic stir bars does this for you
- **IMPORTANT**: FOR ADP, TRAP AND COL TESTS USE NORMAL SALINE WITH CALCIUM (0.9% NaCl WITH 3mM $CaCl_2$) FOR BLOOD DILUTION
- **IMPORTANT**: FOR ASPI AND RISTO TESTS USE NORMAL SALINE (0.9% NaCl) FOR BLOOD DILUTION
- Tests will have an incubation period after adding blood but before adding reagents.
- When the program beeps, it is time to add the reagents as directed by the program.
- Tests are quick. You will have your result in 6 minutes.

AFTER THE TEST

- Print results, write your initials on the hardcopy and make notes as needed.
- Enter results into PROPPR online database, *Openclinica*.
    - See **SOP- Lab Data Entry Procedures** for data entry protocol.
- File the hardcopy accordingly in Research Record Binder on the bookshelf.

CLEANUP AFTER TESTS COMPLETED

- Unplug all used test cells
- Return the sensor cables into the 'parked' position
- Discard of used test cells/pipette tips in the biohazard waste bin.

RESOURCES:

- Multiplate Manufacturer's Handbook

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SOP TITLE: LAB DATA ENTRY PROTOCOL	Version # 1
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PURPOSE: To outline the steps necessary to enter subject data for the PROPPR study.

SCOPE: Applies to the procedure for entering subject at each sample time. These results are run for research purposes ONLY. The results are never used for clinical purposes.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform testing and data entry.

SUMMARY OF THE PROPPR RESEARCH LAB DATA ENTRY

1. Each site enters patient blood collection info into **Openclinica** subject data base (from biospecimen collection form)
2. Each site enters patient TEG + MULTIPLATE data (results) into **Openclinica** subject data base.
3. Each site enters shipping info for shipped fresh samples into **Openclinica** administrative data base (info from daily biospecimen shipping form).
4. Each site enters shipping info for shipped frozen samples into **Openclinica** administrative data base (info from monthly biospecimen shipping form).
5. Upon receiving samples (fresh and frozen) UT Core Lab enters received data into **Openclinica** administrative data base
6. Upon receiving frozen samples from sites UT core lab enters received samples info (info from biospecimen monthly receiving form) into **FreezerWorks** data base.

RESOURCES:

- Houston DCC Protocol

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SOP TITLE: PACKING AND SHIPPING BIOSPECIMENS	Version # 2
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PURPOSE: To outline the steps necessary for the PROPPR study biospecimens to ensure that samples are packed and shipped efficiently, correctly and safely.

SCOPE: Applies to the procedure for packing and shipping subject blood samples at each sample time point where sufficient blood is collected. These samples are for research purposes ONLY.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform testing.

DAILY BIOSPECIMEN PACKING AND SHIPPING (BCT Tube):

- Immediately after collection, gently invert the tube 10 times. Leave it at room temperature until ready to ship to UT Houston Core Lab.
- The lavender/grey top BCT tubes collected MONDAY through THURSDAY are to be shipped within 24h via overnight courier to the UT Houston Core Laboratory. **Thursday collections that occur too late for Thursday shipment should be shipped on Monday morning.**
- **DO NOT ship on Fridays**.
- For the samples collected late Thursday through Sunday, please ship on Monday morning.

LAB SPECIMEN SHIPPING REGULATIONS

- Laboratory patient specimens for PROPPR must be packaged and shipped following IATA Dangerous Goods Regulations (www.iata.org/whatwedo/cargo/dangerous_goods/index.htm) and the 49 CFR guidelines imposed on laboratories and are related to specimen classification, packaging, labeling, documentation, and the proper training of staff.

- It is the responsibility of the send-out staff to follow regulations, and each site's responsibility to train individuals to follow the regulations.
- IATA/CFR Dangerous Goods regulations. **www.mayomedicallaboratories.com/education**
- **Click on Type: Dangerous Goods**
- There are five modules for review and PDF versions of the sessions are available.

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PACKAGING INSTRUCTIONS:

- Place the BCT tubes in the 3 or 8 tube (depending on what your site has ordered) ThermoSafe® Diagnostic Specimen Mailing container, and tape the container securely shut with packing tape (see figure 1)
    - Place each ThermoSafe® Diagnostic Specimen Mailing container in a gallon size plastic Ziploc bag and seal. This will serve as a secondary leak guard.

Figure 1

or

- Shipping containers are tested and certified for transport of diagnostic specimens in conformance with IATA Packing Instruction 650, U.S. Postal Service and DOT regulations.
- **Layer packed tubes in the second insulated shipper container (see figure 2) in the following order**:
    - Place a cool pack at the bottom of the Tegrant® ThermoSafe® Insulated Shipper Multipurpose Container.
    - Place three to four paper towels (for insulation) over the cool pack.
    - Record the number of samples on the Specimen Shipping form.
    - Insert the specimen container with BCT tubes in plastic bags in the shipping box.
    - Place three to four paper towels over the specimens, separating them from the cool packs.
    - Place the cool pack at the top.
    - Try and fill any excess space in shipping container with absorbent material, i.e. paper towels. The less air space in the box, the more likely the temperature will remain stable (see figure 3).
    - It is important to not have too many cool packs, as the samples may freeze; **no more than 3 cool packs per shipping container.**

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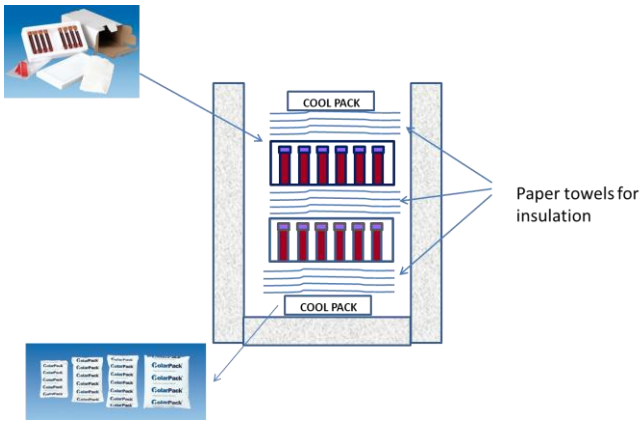
Figure 2

- The refrigerant pack should be frozen in a regular freezer, prior to use. Frozen cool pack helps keep specimens from becoming too warm.
- Place a paper copy of the biospecimen form entitled **"PROPPR Biospecimen Daily Shipping Form"** and biospecimen collection form entitled "**PROPPR Biospecimen Collection Form"** in a plastic bag on top of the packing material.
- Seal the box tightly with strapping tape. Affix a **Exempt Human Specimen** sticker someplace visible on the top of the box, as well as a fully completed Federal Express airbill (or your sites specific shipper) to the outside of the box (see **SOP Appendix** for example of completed air bill)
    - With each Tegrant® ThermoSafe® Insulated Shipper Multipurpose Container, there are three pre-made labels: **Dry Ice, 9, UN1845 label, Infectious Substance,6, UN2812 label and a sender/sendee label.**
    - For PROPPR, you will only use the **Dry Ice, 9, UN1845 label** and **only when sending monthly frozen samples.** You will also need to affix an "**Exempt Human Specimen" label for all boxes sent (BCT 24h and Monthly batch shipments)**

Figure 3:



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    - Contact **Federal Express** (1-800-GO-FEDEX or your sites specific shipper) for pickup or use your institution's mailing services
- Enter the **tracking log information** into the Openclinica administrative data base when you ship the samples.
- Keep the original completed shipping log at your site.
- **Send an email (yao-wei.w.wang@uth.tmc.edu; Brittany.S.Hula@uth.tmc.edu; nena.matijevic@uth.tmc.edu;) with Fedex/shipment tracking number** to notify the Core Lab of shipment. Lab will send confirmation email upon receiving the shipment.
- **Houston Lab Core Contacts**
    - Willa Wang- Yao-Wei.W.Wang@uth.tmc.edu;
        - 713-500-6790
    - Brittany Shea Hula- Brittany.S.Hula@uth.tmc.edu
        - 713-500-6779
    - Nena Matijevic- Nena.Matijevic@uth.tmc.edu
        - 713-500-6807

Mailing Instructions:

All daily (Cyto-Chex BCT lavender/grey tubes) shipping containers are sent to the UT Houston Core Lab by an overnight courier (Federal Express) to ensure receipt by 10:00AM the next morning. **Please request for "room delivery" when shipping. See appendix for an example how to fill out the Fedex shipping form**

Ship containers to the UT Houston Core Lab addressed as follows:

CeTIR Hemostasis Laboratory
Attn.: Willa Wang/Nena Matijevic
The University of Texas Health Science Center - Houston
6431 Fannin Street
Medical School M.S.B. 5.434
Houston, TX 77030

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PACKAGING AND SHIPPING FROZEN BIOSPECIMENS MONTHLY:

Packaging Instructions (Frozen specimens)

- The frozen plasma samples are packed and shipped in freezer boxes, with separators (see figures 4 and 5. Fig 4 shows recommended templates of how to put the frozen samples in the 81-well freezer boxes. Please try to pack frozen samples according to templates.
    - Place a 2-inch layer of dry ice on the bottom of the each Tegrant® ThermoSafe® Insulated Shipper Multipurpose Container.
        - To avoid burns, always wear cloth gloves and safety glasses when handling dry ice.
        - Pellet dry ice is preferred. Block dry ice must be reduced to small pieces (1"-2") to minimize the chance of damage to bags and vials.
    - Locate the frozen specimens (freezer boxes)
    - Record the number of frozen specimens on the **Biospecimen Monthly Shipping Form**
- Secure the lids of sample freezer boxes with packing tape, place sample freezer boxes containing frozen samples into a plastic bag, and then into the Shipping container on top of the dry ice.
- Stack freezer boxes only up to the line marked on inside of Shipping container (about two boxes high) Cover them with more dry ice (on top of and around the sample boxes).
- Do not overfill, leaving enough room at the top to put the lid on securely.
- Use a minimum of 5-8 pounds of dry ice per shipment (more if needed during the hottest months of the year).
    - Place packing material (or paper) (do not use "packing peanuts") on top of the dry ice to fill the box.
    - Place a paper copy of the Biospecimen Shipping Form entitled "**PROPPR Biospecimen Monthly Shipping Form"** and a Biospecimen Collection Form entitled "**PROPPR Biospecimen Collection Form)** in a plastic bag on top of the packing material.
    - Seal the box tightly with strapping tape. Affix a **Dry Ice, 9, UN1845 label**, an **Exempt Human Specimen label** and completed Federal Express (or your sites specific shipper) air bill (see **SOP Appendix** for how to properly fill out the air bill) to the outside of the box.
        - With each Tegrant® ThermoSafe® Insulated Shipper Multipurpose Container, there are three pre-made labels:**, Dry Ice, 9, UN1845 label, Infectious Substance,6,UN2812 label and a sender/sendee label.**
        - For PROPPR, you will only use the **Dry Ice, 9, UN1845 label** and **only when sending monthly frozen samples.** You will also need to affix an "**Exempt Human Specimen" label for all boxes sent (BCT 24h and Monthly batch shipments)**
        - **Write all the relevant information and the approximate weight of the Dry Ice on the Dry Ice, 9, UN1845 label and on the Fed Ex air bill.**

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Figure 4.

a) Screen Failures (18 patients/box)

R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5
R2	R3	R4	R5		R2	R3	R4	R5

b) Randomized (3 patients/box)

R2 (0hr)	R3 (0hr)	R4 (0hr)	R2 (0hr)	R3 (0hr)	R4 (0hr)	R2 (0hr)	R3 (0hr)	R4 (0hr)
R2 (2hr)	R3 (2hr)	R4 (2hr)	R2 (2hr)	R3 (2hr)	R4 (2hr)	R2 (2hr)	R3 (2hr)	R4 (2hr)
R2 (4hr)	R3 (4hr)	R4 (4hr)	R2 (4hr)	R3 (4hr)	R4 (4hr)	R2 (4hr)	R3 (4hr)	R4 (4hr)
R2 (6hr)	R3 (6hr)	R4 (6hr)	R2 (6hr)	R3 (6hr)	R4 (6hr)	R2 (6hr)	R3 (6hr)	R4 (6hr)
R2 (12hr)	R3 (12hr)	R4 (12hr)	R2 (12hr)	R3 (12hr)	R4 (12hr)	R2 (12hr)	R3 (12hr)	R4 (12hr)
R2 (24hr)	R3 (24hr)	R4 (24hr)	R2 (24hr)	R3 (24hr)	R4 (24hr)	R2 (24hr)	R3 (24hr)	R4 (24hr)
R2 (48hr)	R3 (48hr)	R4 (48hr)	R2 (48hr)	R3 (48hr)	R4 (48hr)	R2 (48hr)	R3 (48hr)	R4 (48hr)
R2 (72hr)	R3 (72hr)	R4 (72hr)	R2 (72hr)	R3 (72hr)	R4 (72hr)	R2 (72hr)	R3 (72hr)	R4 (72hr)

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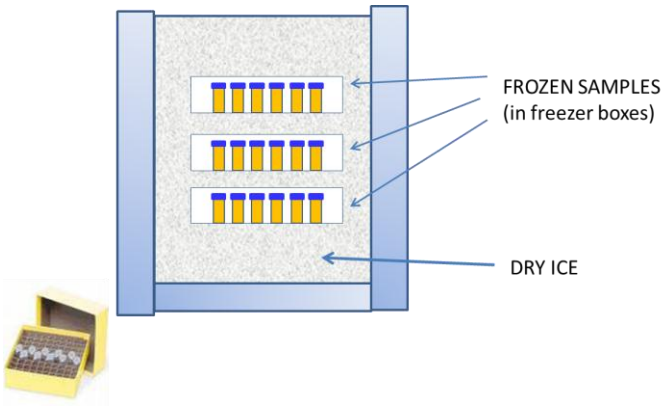
Figure 5.



- Contact Federal Express (1-800-GO-FEDEX or your sites specific shipper) for pickup or use your institution's mailing services.
- Enter the tracking log information into the Openclinica administrative data base when you ship the samples.
- Keep the original completed shipping log at your site.
- Send an email (Yao-Wei.W.Wang@uth.tmc.edu; Brittany.S.Hula@uth.tmc.edu; Nena.Matijevic@uth.tmc.edu) with Fedex (or your sites specific shipper) **tracking number** to notify the Core Lab of shipment.
- ** **For frozen samples, please ship on Monday through Wednesday only****

Mailing Instructions:
All shipping containers are sent to the UT Houston Core Lab by an overnight courier (Federal Express) to ensure receipt by 10:00AM the next morning. **Please request for "room delivery" when shipping. (See SOP Appendix for an example of FedEx shipping form.)**

Ship containers to the UT Houston Core Lab addressed as follows:

CeTIR Hemostasis Laboratory

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Attn: Willa Wang/Nena Matijevic

The University of Texas Health Science Center - Houston
6431 Fannin Street
Medical School M.S.B. 5.434
Houston, TX 77030

SHIPPING AND PACKING NECCESSITIES

BCT 24 h samples-
ThermoSafe® Diagnostic Specimen Mailing container (3 or 8 tube)
Packing Tape
Gallon Ziploc Bags
Paper Towels
Up to 3 Polar re-freezable ice packs
Tegrant ThermoSafe Insulated Shipper Multipurpose Container
PROPPR Daily Biospecimen Shipping Form
PROPPR Daily Biospecimen Collection Form
Exempt Human Specimen label
Fully executed FED EX Shipping Air bill

Monthly Specimens-
Freezer tube boxes with separators
Packing Tape
Gallon Ziploc Bags
Paper Towels
5-8kg of Dry Ice
Tegrant ThermoSafe Insulated Shipper Multipurpose Container
PROPPR Monthly Biospecimen Shipping Form
PROPPR Monthly Biospecimen Collection Form
Exempt Human Specimen label
Dry Ice, 9, UN1845 label
Fully executed FED EX Shipping Air bill

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PROPPR Lab Shipment Log:

Use this log to record research lab sample shipments to the CORE research lab. Keep one copy for yc site records and include 1 copy with the lab shipment. Print a new form for each shipment. Refer to La MOO for packaging and shipping information.

Date of Shipment: ___ / ___ / ___ Shipment Tracking Number:_____

(For Houston Site Only, Record Today's Date)

Lab Sample ID Number or Bar Code Label	Lab Sample ID Number or Bar Code Label	Lab Sample ID Number or Bar Code Label

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: QUALITY CONTROL FOR RESEARCH LABS	Version # 1
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PURPOSE: To outline the steps necessary to run the quality control in the clinical lab to ensure the most accurate outcomes are obtained.

SCOPE: Applies to the procedure for quality control in daily basis monthly basis.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform clinical lab testing.

MATERIALS, REAGENTS AND EQUIPMENT:

- ACL TOP Fully Automated Coagulation Analyzer
- ELISA microplate reader E max Precision Reader, Molecular Devices; ELISA washer BioTek Elx50.
- FLUOROSKAN (Thermo) analyzer supplied with excitation filter (390 nM) and emission filter (460 nM) and Thrombinoscope™ software dedicated to thrombin generation measurement (Maastricht, Netherlands).
- Gallios™ flow cytometer

PROCEDURES:

PROPPR RESEARCH LABS QUALITY CONTROL

1- COAGULATION

Instrument specifications: ACL TOP Fully Automated Coagulation Analyzer (Inctrumentation Laboratories, Beckman Coulter, Miami, FL) with clotting, chromogenic, and immunoturbidimetric assay capabilities.

- Complete solution for both routine and specialty testing
- Continuous operation, with access to samples, reagents and cuvettes at any time
- STAT samples to introduce at any time, in any position
- Barcoded reagents for safe and fully automated materials management
- Sophisticated onboard QC package
- Fully automated rerun, reflex, and factor parallelism testing
- Results management including clot curves display and auto-validation program
- Automated reagent management, quality control and maintenance.

All assays are performed as instructed in the manufacturer's procedure manual including the performance of quality control.
Lyophilized calibration plasma, prepared from pooled citrated plasma from healthy donors, is used to construct calibration curves for those assays reporting in a calibrated reporting unit. The calibration plasma values used to establish the curve are traceable to the standards supplied by the National Institute for Biological Standards and Controls (NIBSC) according

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to the WHO recommendations. Each calibration curve consists of multiple dilutions of the calibration plasma assayed and processed by the instrument in a manner similar to processing a sample. New calibrations are performed with each change in reagent lot, and any change in the instrument.

Quality control material consists of normal and/or abnormal pre-assayed lyophilized plasma for the quality control of coagulation assays in the normal or abnormal ranges. It is run daily for monitoring of the daily performance of the assays.

Sample: citrated plasma

2- ELISA assays

All ELISA assays are performed according to manufacturer's instructions.
Instrument specifications: ELISA microplate reader E max Precision Reader, Molecular Devices; ELISA washer BioTek Elx50.

Calibration curves are constructed with each run using standard material provided, according to instructions. Quality control material is either provided with each kit or, alternatively, lyophilized normal control plasma is used.

Sample: citrated plasma

3- CALIBRATED AUTOMATED THROMBOGRAM (CAT)

CAT is a comprehensive system to measure thrombin generation based on fluorescence according to the Hemker and al. method.
Instrument specifications: FLUOROSKAN (Thermo) analyzer supplied with excitation filter (390 nM) and emission filter (460 nM) and Thrombinoscope™ software dedicated to thrombin generation measurement (Maastricht, Netherlands).
Thrombin calibrator is used in each experiment and with all samples. The use of thrombin calibrator for each individual plasma corrects for donor-to-donor differences in plasma color, inner filter effect and substrate consumption. After the measurement the program calculates all parameters of the Thrombogram (area under curve, peak height, lag time and more) and expresses the results in nanomolar thrombin in time.

Quality control material consists of the normal lyophilized plasma which is run along with patient samples for monitoring of the assay performance.

Sample: citrated plasma

4- FLOW CYTOMETRY

Instrument specifications: The Gallios™ flow cytometer (Beckman Coulter, Miami, FL) with three solid-state lasers in standard red and blue, and violet. It provides efficient acquisition of superior quality data from up to 10 colors with advanced optical design for enhanced sensitivity for multicolor assays. It uses Kaluza® analysis software which is a revolutionary flow cytometry analysis software solution designed for high content data. Kaluza employs technology that allows for real time analysis of high content files.
Instrument quality control material includes fluorescent microspheres (Flow Check) used daily to validate instrument optical alignment and fluidic system. Biological controls are pre-assayed stabilized human blood cells with target value for various cell populations for validation of operating system and methodology of immunophenotyping. Positive procedure control sample serves to determine whether procedures for preparing and processing the specimens are adequate, and to test labeling efficiency of new batches of monoclonal antibodies. A long term stabilized blood specimens (Immuno-trol) validated for this purpose is used. They are assayed for lymphocyte, granulocyte and monocyte specific antigens and single platform absolute counts. Light scatter, population distribution, fluorescence intensity, and antigen density mimic those of whole blood.

To asses cell viability a separate staining is performed using 7-AAD counterstained with CD45. A minimum viability of 75% is recommended.

Sample: stabilized whole blood (CytoChex BCT tube)

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: QUALITY CONTROL FOR TEG MACHINE	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: To outline the steps necessary to run the quality control on the TEG machine and to ensure the most accurate quality control is obtained.

SCOPE: Applies to the procedure for quality control in weekly basis.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform TEG testing.

LOCATION OF TEG MACHINE: The TEG machine should be conveniently located near the ED, OR and ICU to allow the Research Staff to run the samples in an expedited manner. In addition, the reagents must be kept in a refrigerator located near the TEG machine.

MATERIALS, REAGENTS AND EQUIPMENT:

TEG machine
Refrigerator/freezer
TEG Hemostasis System Level I/II Control
Pins/Cups (as one unit)
Pipette (will need 2 sizes, P-20 & P-1000)
Pipette tips (will need 2 sizes, 1mL and 20uL)
Small biohazard plastic container to dispose of contaminated pipette tips in-between test steps
Protective equipment (gloves, eye protection, lab coat)

OVERVIEW:

1. Take all needed reagents out of the fridge to warm to room temperature.
2. Check volumes and expiration dates, and thaw or open new reagents as needed.
3. Reconstitute the Level I/II Control.
4. Record any old results and clear all channels to be used.
5. Input lot number which located on the QC tube at the patient number position.
6. Select L1 if using level 1 control QC tube or select L2 if using level 2 control QC tube.
7. Set up cups, pins, and test cells for each channel. (should be two channels per machine)
8. Run tests in order of test priority list below.
9. Once tests start successfully, dispose of used pipet tips.
10. As tests are completed, print/record results and clear channels.
11. Dispose of used cups/pins/test cells and any leftover blood.
12. Check sharps, biohazard disposal.
13. Shred any leftover protected health information.

SPECIAL NOTES:

COMPUTER SYSTEM Log-in Information
Startup computer
Login to computer system:
Username: TEG
Domain: XXXXX
Password: XXXX
Click on TEG V4 Icon on desktop:

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User name: XXXXXX
Password: XXXX
Once TEG Program starts, will ask for user:
User: XXXX
Password: There is no password. Simply hit 'enter'

REAGENTS:

Reagents located in labeled boxes in the refrigerator

PIPETS / PIPETTE TIPS

Standard laboratory handheld pipets and pipet-specific tips are used. The electronic pipettor associated with the Multiplate machine will not fit most standard laboratory pipets.

CUPS/PINS

Located next to the machine

Pins are held within the small plastic cup. Do not touch the pin. Only hold by the outside of the cup when handling.

PROCEDURES:

PRE-QC REAGENT PREPARATION

Level I/II Control vial

1. Allow the control vials to reach room temperature by incubate in room temperature for 5 minutes.
2. Make sure the lyophilized powder is on the bottom of the vial; you may need to tap the vial a few times.
3. Remove the cap of the lyophilized control.
4. Into each vial of lyophilized control, slowly pour 1 vial of 1ml of diluent water (Green cap), provided. Make sure no water drips out.
5. Screw the cap back on to the vial of the control.
6. Shake the vial vigorously and then let it stand for 5 minutes at room temperature.
7. Shake the vial vigorously and let stand 5 more minutes.

0.2M CaCl2

Found in the Level I/II Control boxes in the refrigerator.
Store at room temperature once opened.
If out, prepare CaCl2 solution on bench top:
Solution: 0.2M CaCl2 in NaCl
Add 200ul of 1M CaCl2 solution to 800ul of 0.9% sodium chloride ("normal saline")
Mix by pipetting.
Store at room temperature

REAGENT STORAGE

Each reconstituted control is viable for 2 hours at room temperature.
Storage temperature: 2°C – 8°C, unopened vials stable to expiration date.

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: QUALITY CONTROL FOR TEG MACHINE	Version # 1
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TEST PREPARATION

Supplies, Machine and Level I/II control ID Entry

Reagents must be kept in the refrigerator.

Allow Level I/II Control to sit at room temperature for 5-10 minutes before starting test.

Check the bubble level on top of the TEG machine:

If the bubble is not in the center of the bullseye, the machine is not level; rotate the adjustable legs on either side of the bottom front of machine to straighten until bubble is in center of target.

To run a test, click the TEG icon located in upper right side of the toolbar.

The screen will show the 2 channels with drop-down menus for test, patient ID, and sample ID for each channel.

Test Name: Go to the drop down menu on the left that shows "---N- Test"

1st channel: Level I/II Control

2nd channel: Level I/II Control

Patient ID:

Type in the lot number printed on the tube of the Level I/II Control

Cup/Pin Set-up (IMPORTANT as this is the cause of many issues with tests)

The cup/pin level should already be in the load position.

This is the way the machine should be left after a test.

Slide white platform down until you hear a click, but NOT all the way down to the base of the machine.

If pushed all the way down, it will prevent the cup from loading properly.

Place the cup/pin into the platform slot.

While HOLDING ONTO the top of machine so it doesn't know over (easy to do), slide the white platform with cup/pin up into black loading cylinder on machine.

Once the platform is all the way up, press the white button on the base of the platform 3 times to secure the pin.

Once the pin is in place, pull the platform back down about halfway, and NOT all the way to the bottom.

Hold the bottom of platform with two fingers, and push down on the rim of the cup with your thumbs to securely seat the cup.

Don't push platform all the way down or you won't be able to properly seat the cup.

TEST PROTOCOL

1. In the software, select the sample type L1.
2. Load a plain cup and pin into each TEG analyzer column.
3. Prepare reagents as described above.
4. Invert the vial 5 times.
5. Pipette 20ul of 0.2M calcium chloride into each TEG cup.
6. Pipette 340ul of reconstituted control into each cup.
7. Immediately slide the carrier up and move the lever to test.

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8. Start the test in the TEG Analytical software by clicking the green arrow.
9. Run until MA is finalized.

DURING THE TEST

To view test progress:

From TEG screen, click 'Done'
This will take you to the tracing review menu.
To return to regular TEG screen, click the TEG button (looks like belted penguin) at top of screen again.

AFTER THE TEST

Once test are complete, go to tracing review screen by clicking on 'Done' from TEG channel setup screen;
To view individual tracing, double-click it.
To return to tracing review screen, double-click the tracing
Read the control parameters which stated in the product sheet, the parameters should be within their appropriate ranges.
DO NOT report any patient results until the control parameters are within their appropriate ranges.
While in full-screen tracing view mode, click "Print" in upper left corner.
Check the result and make sure that the result fit into the appropriate range.

CLEANUP AFTER TESTS COMPLETED

To eject up/pin:

Move silver lever to "load" position.
Push lever down to eject the cup & pin together.
Push the white platform all the way down past the first click to the base of the machine; this will eject the cup.

Discard used cups/pins/pipette tips in the biohazard waste bin.
Leave platform up and lever in load position when TEG not in use.

RESOURCES:

- TEG Manufacturer's Operation Manual and Manufacture Product Sheet

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: QUALITY CONTROL FOR MULTIPLATE MACHINE	Version # 1
SOP NUMBER:	Page 1 of

PURPOSE: To outline the steps necessary to run the electronic quality control and liquid controls on the MULTIPLATE machine and to ensure the most accurate quality control is obtained.

SCOPE: Applies to the procedure for electronic quality control in daily basis and liquid controls QC on monthly basis.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform MULTIPLATE testing.

LOCATION OF MACHINE: The MULTIPLATE machine should be conveniently located near the ED, OR and ICU to allow the Research Staff to run the samples in an expedited manner. In addition, the reagents must be kept in a refrigerator located near the MULTIPLATE machine.

MATERIALS, REAGENTS AND EQUIPMENT:
MULTIPLATE machine
Protective equipment (gloves, eye protection, lab coat)

OVERVIEW:
1. Log-in to the computer.
2. Make sure all of the ports are secure at their own position.
3. As tests are completed, print/record results for record.
4. Shred any leftover protected health information.
5. Enter results into database.

SPECIAL NOTES:
COMPUTER SYSTEM Log-in Information
Startup computer
Login to computer system:
Username: Multiplate
Password: XXXXX

PROCEDURES:

TEST PROTOCOL: ELECTRONIC CONTROL

1. Make sure all of the sensor cables are secure in the “parked” position -- if they are not at their right position, the test result will be off.
2. In the computer, move your arrow towards the top of the left hand corner and select the electronic control icon.
3. Select the start electronic control icon.

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4. Wait for 5-10 minutes, the QC program is running.
   The screen will show 'The electronic control was successful for the following channel'. If there is a problem, the screen will show 'The electron control was out of reference range'; repeat this test, and if the problem persists contact Multiplate technical support staff for assistance.

DURING THE TEST

To view test progress:

The screen will show you the progress of the test.

AFTER THE TEST

Once test are complete, click close and the QC screen will be closed.

RESOURCES:

MULTIPLATE Manufacturer's Operation Manual

TEST PROTOCOL: LIQUID CONTROL SET

PURPOSE: For use as an assayed quality control verification of the resistance measure of impedance aggregometry.

Preheat the reagents for 20 min at 37°C in the preheating positions of the Multiplate® analyzer prior to use. Run measurements for level 1 and level 2 controls as follows:

Level 1
Load all 5 channels with Multiplate® test cells
Attach the sensor cables to the test cells
Add 600 µl of "Solution 1" into each channel
3 min incubation phase (select <F2:Start timer>)
Select **<F3: Start test>** for all channels
select <F2:Start timer> again, and **wait for the first 3 min of measuring time**
Add 100 µl of "Solution 2" **onto** the surface of "Solution 1".
Add 200 µl of "Solution 2" **onto** the surface of "Solution 1".
Do not immerse the pipette tip into "Solution 1" to avoid air bubbles.
Wait for the completion of 6 min test time
Print out and compare aggregation results with expected values

NOTE: It is important to precisely follow this procedure. The use of non-preheated solutions or shorter incubation times may skew results. It is important that "Solution 2" is pipetted onto the surface of "Solution 1".

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: QUALITY CONTROL FOR MULTIPLATE MACHINE	Version # 1
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If results of a liquid control analysis are not within the expected range, repeat the analysis. If a channel's results repeatedly fall outside of the expected range lock the appropriate channel in the Multiplate® software (menu Multiplate -> Channel administration) and contact the manufacturer or local Multiplate® representative for service.

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: MIXING REAGENTS	Version # 2
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PURPOSE: To have ample reagents for processing PROPPR samples

SCOPE: The time sensitive nature of the blood processing necessitates that reagents be pre-mixed and ready to use.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will process the subject blood samples.

TEG/MULTIPLATE Reagents

TEG

TEG kaolin solution:

- Stored in labeled boxes in refrigerator.
- If the kaolin solution cap is unscrewed but the test is aborted without adding blood to the kaolin, write today's date on top of cap and return the rest to the fridge; this can be used in next 24h.
- Kaolin should be spun down in a tabletop centrifuge for a few seconds before use to concentrate all of the reagent to the bottom of tube.

TEG calcium solution: (0.2M CaCl2 in NaCl)

- Once opened, the CaCl2 solution can be stored at room temperature.
- If out of the CaCl2 solution from Haemonetics, calcium solution can also be prepared from a standard laboratory stock solution of 1M CaCl2 on benchtop (see recipe below).
- The TEG and Multiplate calcium solutions contain different concentrations of calcium, and are **NOT** interchangeable.

MULTIPLATE

Lyophilized powders for ADPtest, TRAPtest, ASPItest, and RISTOtest are stored in the refrigerator; once reconstituted and aliquoted as below, the aliquots are stored in the freezer until they are thawed for use.
ADPtest, TRAPtest, ASPItest, and RISTOtest reagent aliquots are stored in refrigerator once thawed.
COLtest reagent is NEVER FROZEN and always stored in the refrigerator.

- **ADP, TRAP, ASPI, and RISTO reagents:**
  - Refrigerator contains the thawed tray of reagent aliquots and the supply of lyophilized reagents to be reconstituted as needed.
  - Check expiration date/time on thawed, aliquoted reagents in the fridge. If expired, toss and thaw a new one.
  - The freezer contains all aliquots of reconstituted reagent.
  - If less than 3 aliquots left in the freezer supply for a particular reagent, reconstitute a new bottle of lyophilized reagent from the refrigerator.
    - Re-suspend the lyophilized reagent in 1mL reagent-grade, ultra-pure water at room temperature and mix gently by pipetting
    - Prepare 1.5mL tube aliquots of each reagent. If reconstituted and kept in a refrigerator, ADP, TRAP, RISTO ASPI reagents are stable for 7 days, except ASPI, which is only stable for 24 hours. If reconstituted, frozen and then thawed,

ADP, TRAP, RISTO ASPI reagents are stable for 24 hours **(see SOP Reagent Expiration Table):**

- For ADP / TRAP reagents: **200uL** (10 tests) per aliquot
- For RISTO reagent: **500uL** (10 tests) per aliquot
- For ASPI reagent: **42uL** (2 tests) per aliquot

- Label the top of each aliquot with the name of the reagent.
- Write your initials and date of reagent preparation on the top of the original reagent bottle.
- Place aliquots in freezer box in a row behind the labeled reagent bottle.

- Once an aliquot is thawed for use, write the date of expiration on the top of the aliquot.
- **Frozen reagents take ~10min to thaw – BE SURE to check the amount of thawed reagent in the fridge before starting a test.**

Multiplate calcium solution: (3mM CaCl2 in NaCl)

- Ordered from Diapharma.
- Storage: Unopened tubes stored in the refrigerator; once opened, the solution tube can be left on the Multiplate block in the holder. Be sure to tightly reseal to avoid evaporative loss.
- The TEG and Multiplate calcium solutions contain different concentrations of calcium, and are **NOT** interchangeable.

Saline solution:

- A standard clinical/laboratory reagent; 0.9% sodium chloride solution ("normal saline"). Taken from clinical IV or stock bottles, common laboratory stock, or purchased from any standard laboratory supply company.
- Stored on the Multiplate block in 3 or 5 mL standard laboratory round-bottomed polystyrene – be sure this will fit into the warmer block. Tightly reseal after each use to avoid evaporative loss.
- To restock: Refill from any bottle or IV solution. MUST BE PRESERVATIVE-FREE.

You should check on a weekly basis on the status of your Reagent supply and any re-ordering that needs to be done. Your specific TEG/Multiplate Sales Support Representative should know what you need and be able to stock any regents that need re-supply.

$CaCl_2$ Recipe

TEG CALCIUM (0.2M $CaCl_2$ in NaCl):
ORDER FROM HAEMONETICS Cat#7003 5ml $5.5 READY TO USE
If you've run out of this, you can also prepare it from a standard laboratory1M CaCl2 stock solution by diluting 200uL of 1M CaCl2 solution in 800uL of 0.9% sodium chloride ("normal saline") and mixing by pipet.

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: MIXING REAGENTS	Version # 2
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MULTIPLATE CALCIUM (3mM $CaCl_2$ in NaCl):
ORDER FROM DIAPHARMA NaCl/3mMCaCl2; CatMP0530# READY TO USE
If you've run out of this, you can also prepare it from a standard laboratory1M CaCl2 stock solution by diluting 3uL of 1M CaCl2 solution in 997uL of 0.9% sodium chloride ("normal saline") and mixing by pipet.

Procedure to prepare the Benzamidine Collection Tubes

Molar Calculation

Molecular weight of Benzamidine = 156.61g
Target concentration in 10ml deionized water solution is 1M
1M x 0.01L = 0.01 moles
0.01moles x 156.61g = 1.5661g
Put 1.5661g of Benzamidine into 0.01L deionized water and mix by inverting.

Procedure

1. Place an empty weighing boat/bowl onto a balance or scale.
2. Press the zero button located on the balance to zero out the weight of the weighing boat/bowl.
3. Use a lab spatula to scoop the Benzamidine powder into the weighting boat until 1.5661g is measured on the read-out of the balance.
4. Pour the Benzamidine powder into a 50ml tube and add 10ml deionized water to it.
5. Mix the solution by inverting the tube a few times.
6. Use foil to cover the 50ml tube as the Benzamidine solution is light sensitive.
7. Use a 1ml syringe with a 26G needle inject to remove 100ul (0.1cc) of Benzamidine solution.
8. Inject the 0.1cc of Benzamidine solution into a 4.5ml 3.2% citrated collection tube.
9. Mix by inverting the tube a few times and label properly. On the label, include the date the tube was created.
10. Repeat steps 7, 8 and 9 for at least one box of tubes.
11. When exposed to light, the tubes with the Benzamidine solution have a shelf life of **4-6 months.**
12. Store the excess Benzamidine tubes that you don't need immediately in a dark cabinet.
13. Always store the jar of Benzamidine powder in a dark cabinet.

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SOP TITLE: MIXING REAGENTS	Version # 2
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Things to know

- Benzamidine (Sigma #434760-25G) is dissolved to make a 1M solution in water. (Ordering information listed in **SOP Supplies Ordering**)
- Reconstituted benzamidine is very light-sensitive; make sure it is always stored in a dark cabinet and a foil-wrapped container.
- For each 4.5ml 3.2% citrated Vacutainer blood collection tube (Fisher # 22-029309), carefully puncture the top with the needle and inject 100ul (0.1 cc) of the benzamidine solution. Do not draw more than 100ul (.1cc) into the syringe at a time, if you try to do multiple injections (tubes) at a time, the vacuum will pull more solution out of the syringe than is needed. In general, be careful to control the syringe plunger to avoid adding too much.
- PUT A RED STICKER ON PREPARED TUBES TO DISTINGISH THEM FROM REGULAR BLUE TOP CITRATE TUBES.

RESOURCES:

- Multiplate Manufacturer's Handbook
- TEG Manufactures Operation Manual

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: REAGENT EXPIRATION TABLE	Version # 2
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REAGENT EXPIRATION

	Reconstituted, 2-8° C	Frozen, -20° C	Room Temp.	Thawed (1 freeze/thaw cycle)
Multiplate test cells	-	-	30 days	-
ADP	7 days	4 wks	-	24 hours
TRAP	7 days	4 wks	-	24 hours
ASPI	24 hours	4 wks	-	24 hours
COL	7 days	-	-	-
RISTOhigh	7 days	4 wks	-	24 hours
TEG- Kaolin (unopened)	30-90 days			

Write date that reagent will expire on each newly opened tube.

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: TEG – Raw Data Export	Version # 2
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PURPOSE: To outline the steps necessary to export raw data files from a TEG database.

SCOPE: Applies to the procedure for data extraction for all tests.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who are familiar with TEG software.

MATERIALS, REAGENTS AND EQUIPMENT:

- TEG Machine
- Thumb drive

OVERVIEW:

Reminder: Exporting the data does not delete it from the database; it simply copies and extracts the data of interest.

1. Open TEG by double clicking on the TEG icon on your desktop.
2. Login as requested.
3. Open the TEG database that contains the patient data of interest.
4. Select all PROPPR tests for a specific patient and export the data into: one CRD file and one VEL file.
5. Rename exported CRD and VEL files "PROPPR STUDY ID"
    a. Example: "PROPPR_1210100"
    b. Use the primary study ID (not the Lab ID or randomized ID).
6. End product: You will have two excel files per patient that contains all time points of test results.
    a. Be sure to open the resulting CRD and VEL files to ensure that the appropriate tests have been exported.

TEG EXPORT PROCEDURE:

1. Open the TEG program and be sure that you have the TEG database of interest open.
    a. TEG recommends starting a new database every 500 tracings, so some patient data may be in a different database than the default database that is currently being used.
2. From the File option on the Main menu (top left corner), select "Export".
3. Then select the appropriate sample option.
    a. The program gives you the option to either dump all tests from the database OR select the tests of interest.
    b. Recommend: Select "Subset" and click "Let me pick samples" and click "Next". This is recommended so that all pertinent tests for a specific patient can be exported together in one file.
        i. If you opted to select the "Let me pick samples" checkbox, it will prompt you to select the tests of interest from each specific patient. Please remember to only save one patient at a time.
        ii. To select a sample for that specific patient, click anywhere in the row to highlight that row.

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: TEG – Raw Data Export	Version # 2
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iii. To select additional samples, hold down the Ctrl key while you select each additional test (ex: 0h, 2h, 4h etc)
iv. When you are finished with your selection of test results, hit "OK"

c. The next screen you will see is: "Export data wizard (2)"
   i. Select "Tab delimited" and then click "Export coordinates to a CRD file" and "Export VCurve to a VEL file". Then click "Next".
d. The final screen prompts you for a filename for the export file. Type the filename of your export file into the File name field, and click Save.
   i. How to name exported files: "PROPPR STUDY ID"
      1. Example: "PROPPR_1210100"
      2. Please use the main study ID (not the Lab ID or randomized ID).
e. After naming and saving (final step of the export process) the data, three files are created: A text file (.txt), a CRD file (.crd), and a VEL (.VEL) file. All three files will be saved in the same location as specified in the final screen where you named your file.
   i. The CRD and VEL are the important files. They contain the raw data in a format that can be opened by Excel.
   ii. You can delete or forget about the text file. This can be used to import into different formats if need be (but not necessary for the purposes of this SOP).
f. Open the CRD and VEL files to confirm that the appropriate patient tests were exported and that the file opens up in Excel. Now save the files again as an Excel files using the main study ID and specify whether the file is CRD or VEL data. In the end, each patient will have two excel files.
      1. Ex: "PROPPR_1210100_CRD.xls" and "PROPPR_1210100_VEL.xls"

TEG EXPORT NOTES:

- When exporting more than one test at a time, the resulting CRD file will be one very long list of numbers with minimal breaks between tests. There will be a horizontal line with identifying test information between each test.
- The long string of test values is fine – as long as all Kaolin tests for a patient are in ONE Excel file.
- Each VEL file will have 9 spreadsheets per patient who had all 8 time points results (one spreadsheet for each time point, plus one with calculated V-curve parameters and graphs)
- For ease of organization, our recommendation is to export all tests for a particular patient together (example: PROPPR_1210100 – 0h, 2h, 4h, etc).
- Tests are listed by Patient ID in the TEG database. The database also displays the date/time the test was run, as well as the channel use to perform the test.
- For sites that run additional assays on TEG in addition to Citrated Kaolin: Unless the test type is included in the Sample Description, you will need to confirm that you are pulling the data for the appropriate test by double checking the file once exported.

DATA ORGANIZATION:

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SOP TITLE: TEG – Raw Data Export	Version # 2
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Each patient should have two excel files that contain all raw data for each TEG Kaolin test at each time point.

Example: "PROPPR_1210100_CRD.xls" and "PROPPR_1210100_VEL.xls"

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: Multiplate Raw Data Export	Version # 1
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PURPOSE: To outline the steps necessary to extract raw data from the Multiplate machine.

SCOPE: Applies to the procedure for extracting the raw data from the Multiplate machine.

PERSONNEL RESPONSIBLE: Principal Investigator, Sub-investigators, Study Coordinator and/or other principal investigator-designated site staff who will perform Multiplate testing.

MATERIALS, REAGENTS AND EQUIPMENT:

- Multiplate machine
- Thumb drive

OVERVIEW:

1. Measurement data is automatically saved in both graphic and XML data files.
2. Copy files of interest from Multiplate XML folder to a thumb drive.
3. Rename data files for each patient at each time point for each specific test (ADP/TRAP/COL/ASPI/RISTO).

HOW TO NAVIGATE MULTIPLATE DATA FOLDER

The data folder is located in: C:\DocumentsandSettings/multiplate/Multiplate/Data OR in the folder named "Data" on the desktop.

1. OPEN the "Data" folder on the desktop.
2. Then open the XML file folder within the Data folder.
3. Tests are organized first by year and then by the day that the test was run:
    a. Example: If looking for a test run on December 31, 2012, select file folder **"2012"** and then within this folder select file folder "**20121231".**
4. Once the day of interest is opened, find the set of tests that correspond to the applicable blood sample and patient. Please make sure that you can see the full file name, as the patient ID is located at the end of the file name. You may need to expand the column.
    a. At each time point, a patient will have the following 5 separate files for each of the agonist tests: ADPtest, RISTOtest, TRAPtest, ASPItest, COLtest.
    b. Sample title of a test file:

2012.12.31 - -22.42.06Kanal1 -1_ADPtest(citratedblood)v1-p-1210255tr.tango0h.xml

    c. For this particular example:
        i. The PROPPR ID of the patient is p-1210255
        ii. The trauma name: tango
        iii. Blood sample collection time point: 0 hour
        iv. Specific agonist test: ADP

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PROPPR STUDY: Standard Operating Procedure

SOP TITLE: Multiplate Raw Data Export	Version # 1
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HOW TO EXPORT FROM DATA FOLDER

1. Highlight the desired files
    a. Each patient will have 5 files per time point.
    b. At each time point, a patient will have the following 5 separate files for each of the agonist tests: ADPtest, RISTOtest, TRAPtest, ASPItest, COLtest
2. Right click and select "copy" to select files of interest
3. Create a master folder on the desktop of Multiplate machine for new exported Excel files.
4. Within master folder, create new folder specific to PROPPR patient ID #
5. Paste selected files into PROPPR patient folder on desktop of Multiplate machine.
6. Copy folder(s) with copied XML test files to the hard drive using a thumb drive.

DATA ORGANIZATION

- For purposes of organizing the data, you can perform all conversion with access to Excel on the Multiplate machine.
- Confirm that all appropriate tests have been exported.
- You will need to SAVE AS one master file as an EXCEL File (Make sure you Save As Type-Microsoft Excel 97/2000/XP (.xls)):
- Save the new excel file as "PROPPR Study ID_Timepoint"
    - Example: "P-1210255_0hour"
    - Please follow this format exactly so that files that can be easily sorted in the future.
    - Each patient will have 5 files per time point.
        - Example: If a patient had 7 full assays run, then they will have 35 XML files that will need to renamed and submitted.
        - At each time point, a patient will have the following 5 separate tabs for each of the agonist tests: ADPtest, RISTOtest, TRAPtest, ASPItest, COLtest
    - Open one agonist file with Excel
        - Save As Type-Microsoft Excel 97/2000/XP (.xls)), Save in current PROPPR ID # folder
        - Go down to bottom tab and double-click on the tab to re-name to the appropriate agonist test name.
- To transfer 5 different excel files into the master file, you must have both the master file and the file to be transferred open.
    - Minimize (not close) Master File before starting
    - To transfer one file to master file, have file to be transferred open
        - In file to be transferred, go down to tab at bottom labeled 'Multiplate'
        - Right click and click on 'move/copy sheet'
        - Click on 'to document' and select master file you want to move file to
        - Click 'move to end position', then 'click ok'
        - Close file you just transferred
    - Maximize Master File which now contain more than one agonist file
        - Go down to tab at bottom, right click 'rename sheet'

Effective Date:	Revision Date:	

PROPPR STUDY: Standard Operating Procedure

SOP TITLE: Multiplate Raw Data Export	Version # 1
SOP NUMBER:	Page 3 of

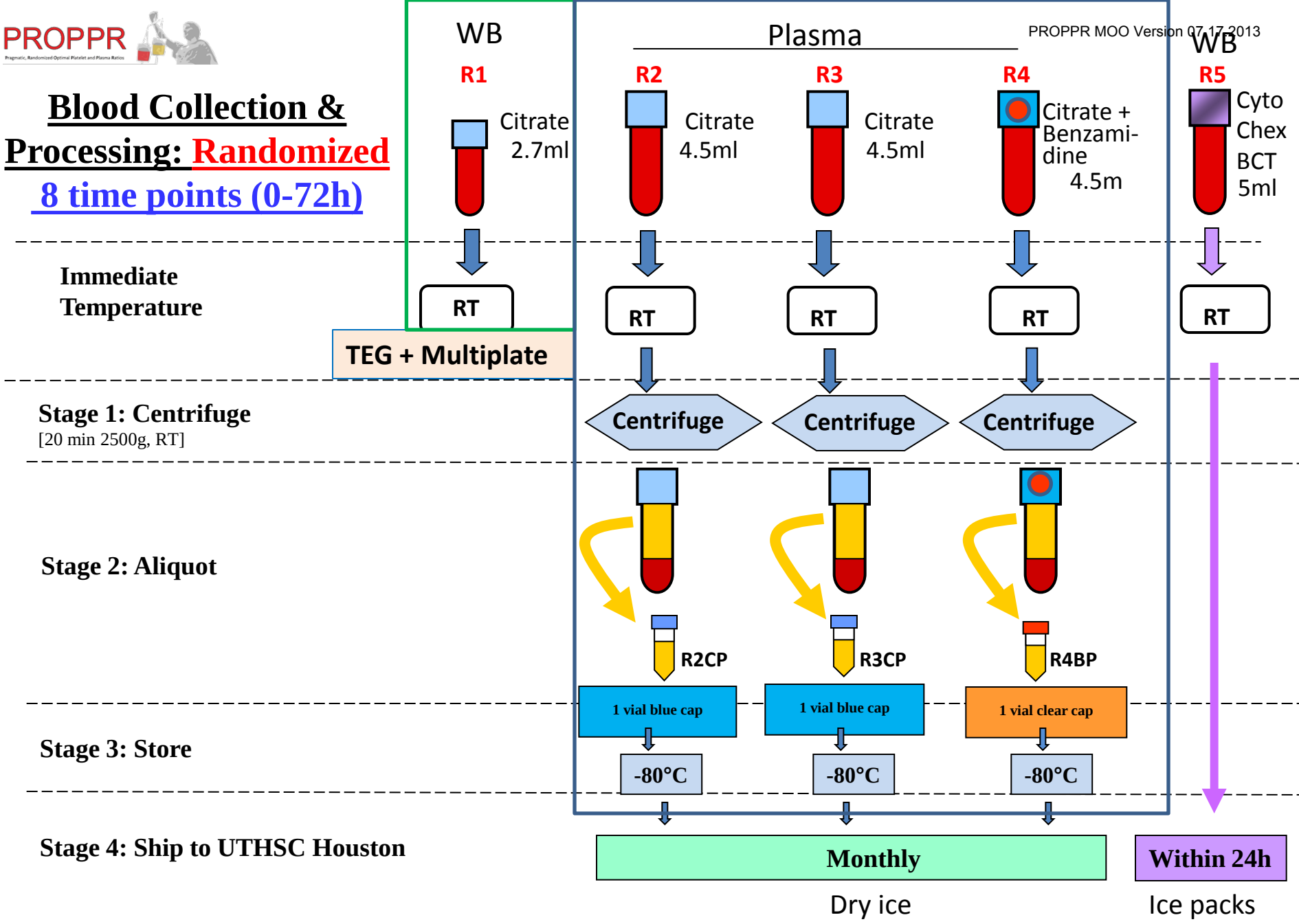
- Rename sheet to specific agonist and time point (example: ADP 0hr) file named. If you can't remember, it is located where 'test name' in the excel file you are working in.

- Repeat above steps for each agonist
- When completed, delete unwanted files in folder
  - Hold CNTRL key down
  - Click on each file to be deleted,
  - Right click and click DELETE
  - Click Yes and then click Yes to All.

Effective Date:	Revision Date:	

Blood Collection & Processing: Randomized

8 time points (0-72h)



TEG® 5000 Thrombelastograph® Hemostasis Analyzer

R1

3 mL

1 mL

1.5 mL

Multiplate® Platelet Function Analyzer

CK= Citrated Kaolin

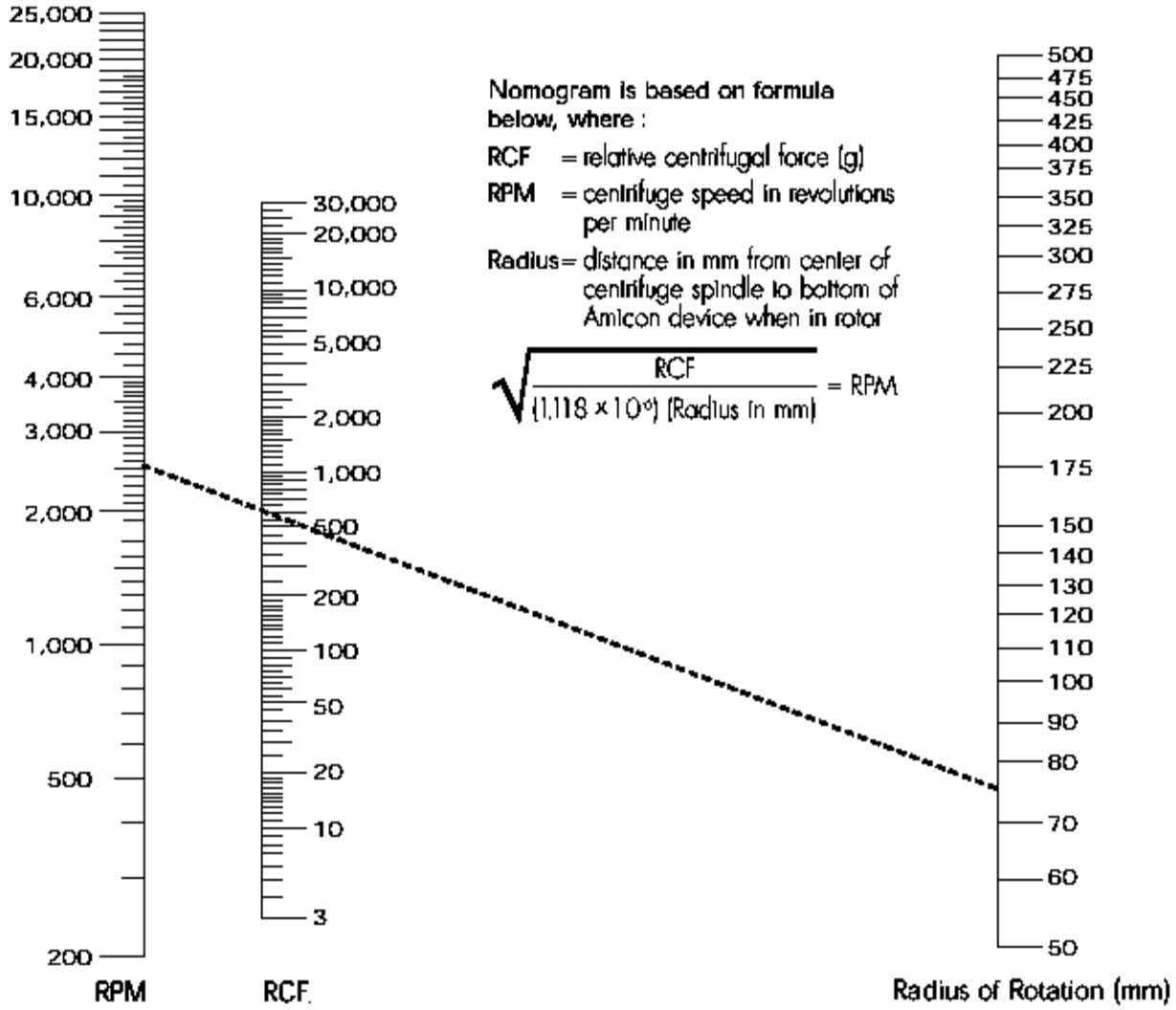
ADP, ASPI, COL, RISTO(H), TRAP

- **TEG and Multiplate trainings will be provided at each site by the manufacturers**

PLT free plasma = 2500g 20min

Use swing bucket rotor

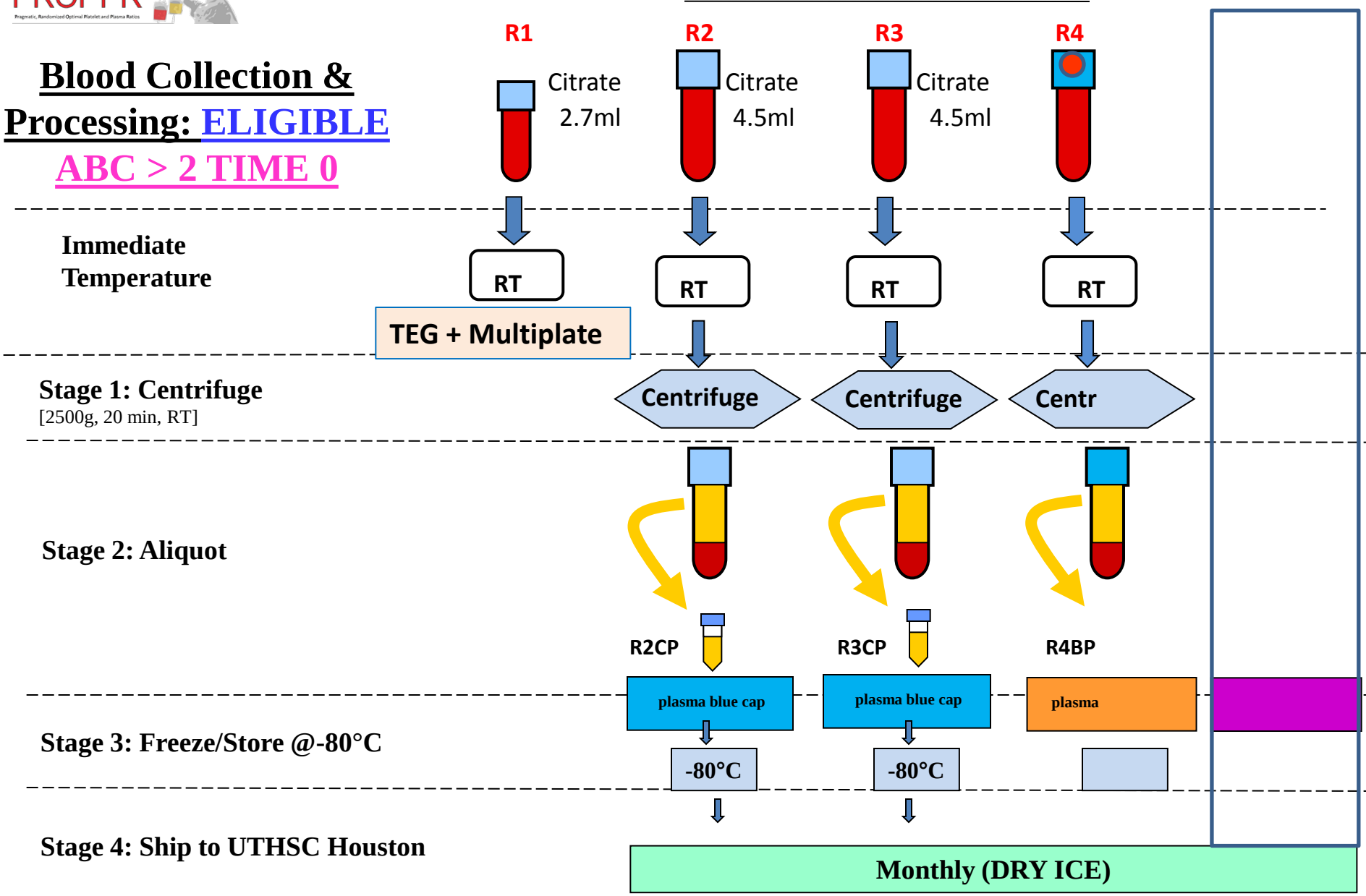
Nomogram for converting maximum relative centrifugal force (RCF, i.e., g-force) to RPM

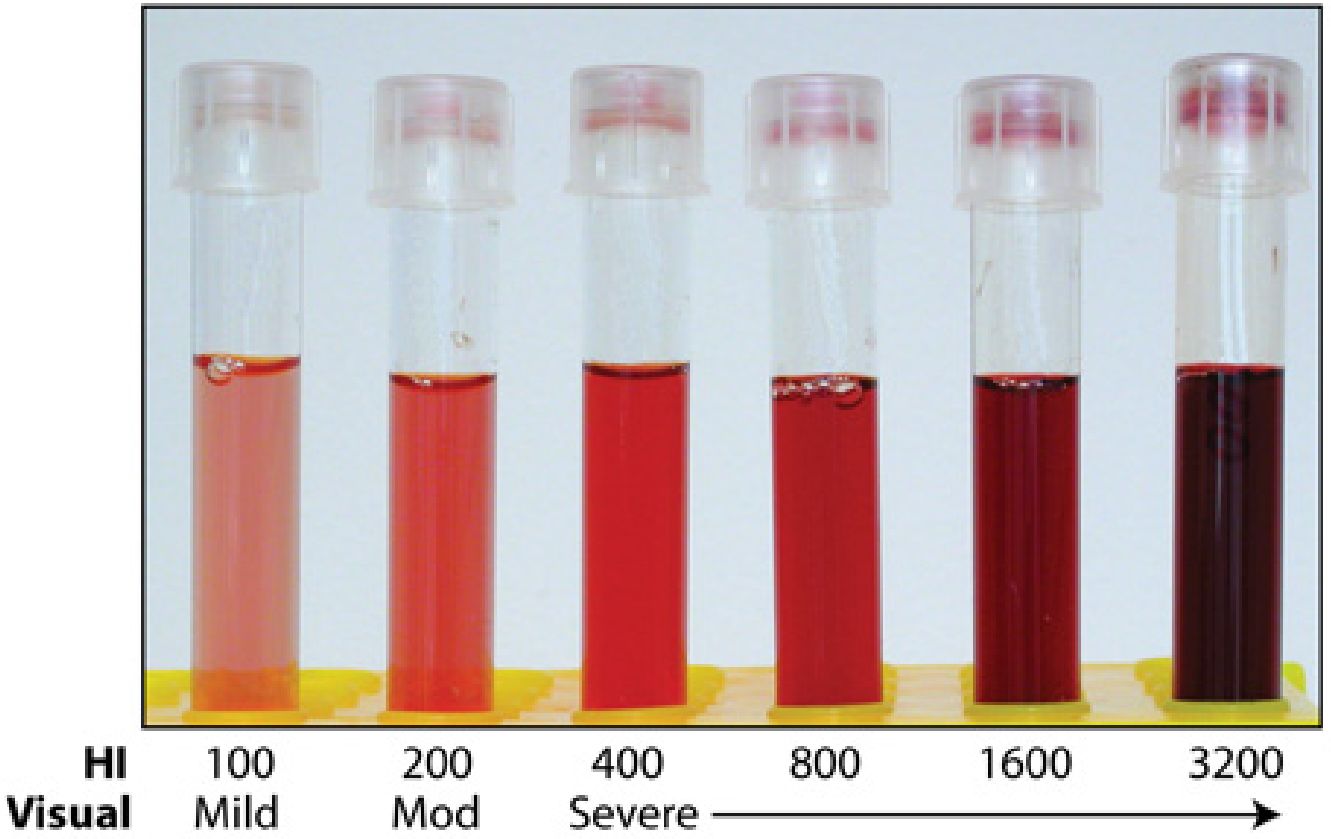


To convert maximum relative centrifugal force (RCF) to RPM: Determine centrifuge 's radius of rotation (in mm) by measuring distance from center of centrifuge spindle to bottom of device when inserted into rotor. Lay a ruler or draw a line from radius value in right-hand column value that corresponds to the device 's maximum rated g-force. Then read the maximum value from column at left.

Blood Collection & Processing: ELIGIBLE

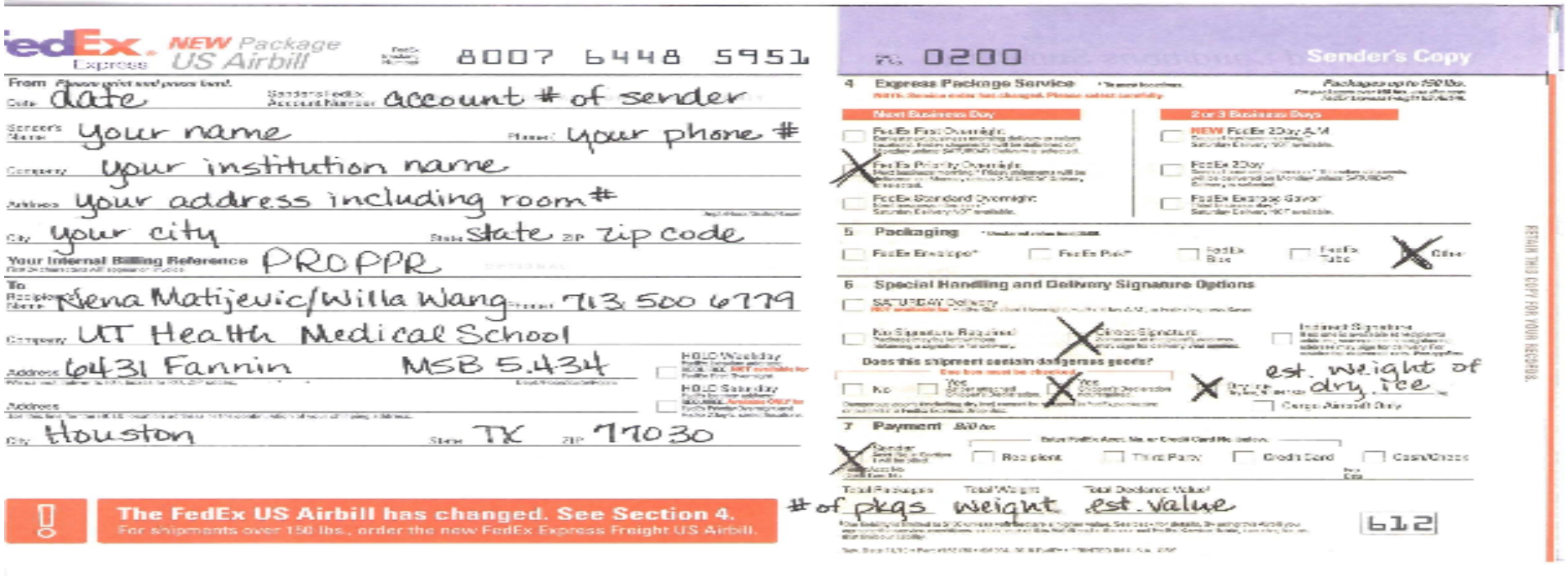
ABC > 2 TIME 0




HI
100
200
400
800
1600
3200
Visual
Mild
Mod
Severe

EXAMPLE FOR SHIPPING SAMPLES WITH DRY ICE

You MUST have a dry ice label properly filled out and attached to your box.



DRY ICE SHIPPING LABEL

You MUST have this label placed on outside of box containing dry ice. Federal Express WILL NOT ship without this label attached to outside of box.

Printable Dry Ice Shipping Label

The label below should print with the proper dimensions of a class 9 hazard label (minimum dimensions: 100mm on a side). Cut around the outside border of the label and affix it to a vertical side of the box (not the top or bottom), oriented as shown below. Many printer inks run when exposed to even small amounts of water, such as rain or snow. Therefore, when using this label, cover with clear plastic tape after filling in all information including the kilogram weight of dry ice.

Shipper's Declaration not Required.

Part B is required

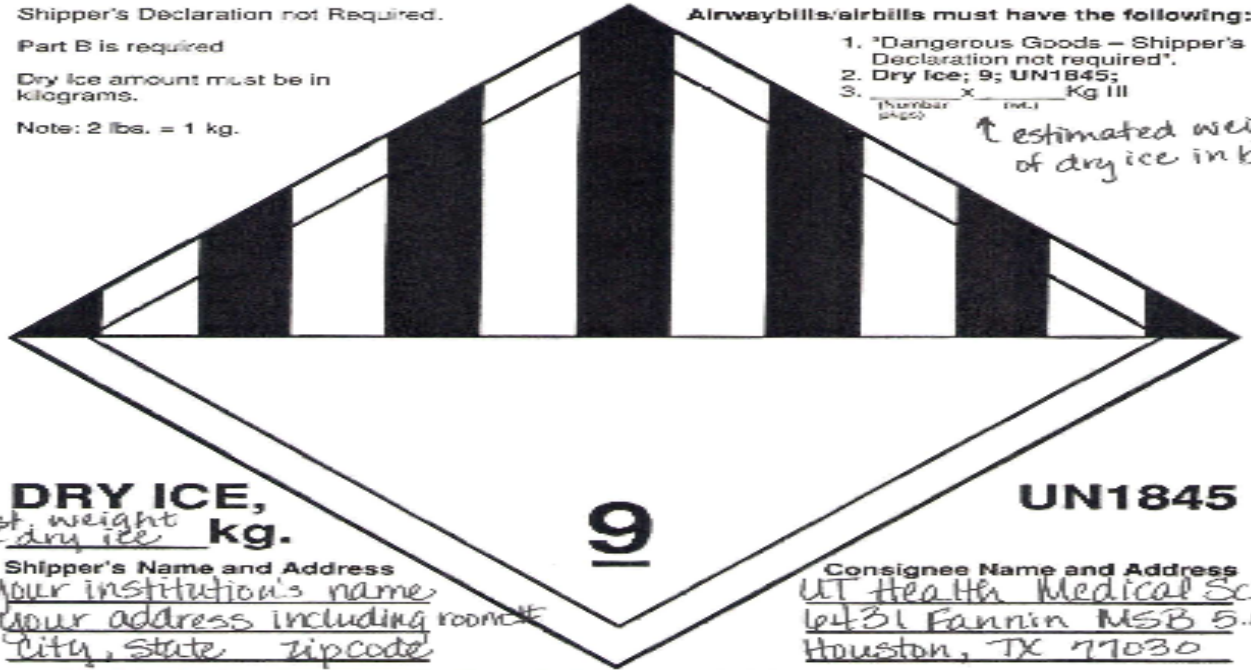
Dry ice amount must be in kilograms.

Note: 2 lbs. = 1 kg.

Airwaybills/airbills must have the following:

1. "Dangerous Goods – Shipper's Declaration not required".
2. Dry Ice; 9; UN1845;
3. _____ x _____ Kg III
   (Number of PKGS) (Wt.)

↑ estimated weight of dry ice in box



DRY ICE, est. weight of dry ice _____ **kg.**

9

UN1845

Shipper's Name and Address

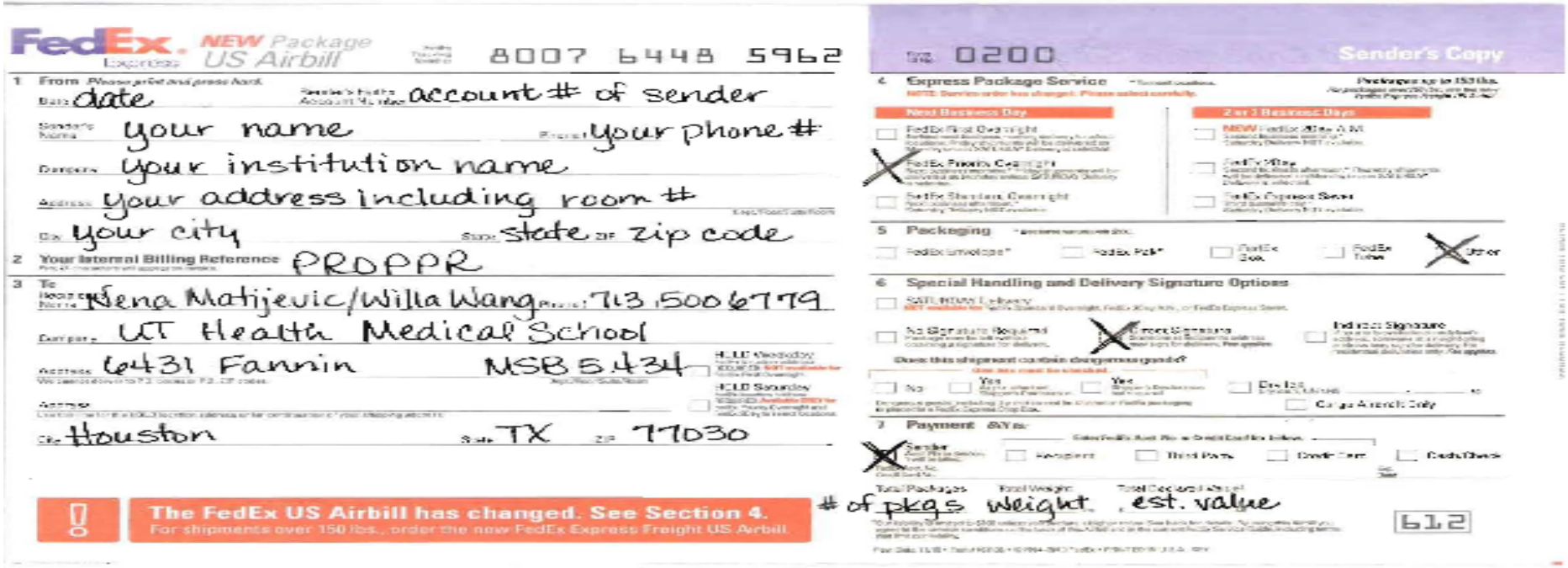
Your institution's name
Your address including room #
City, State Zipcode

Consignee Name and Address

UT Health Medical School
6431 Fannin MSB 5.434
Houston, TX 77030

HML-DI Printed by Labelmaster, An American Labelmark Co.,Chicago, IL 60646 (800) 621-5808

EXAMPLE FOR SHIPPING SAMPLES WITHOUT DRY ICE



3.6.2 Division 6.2 — Infectious Substances

STATE VARIATIONS: AUG-03, CAG-10/11, VUG-02

OPERATOR VARIATIONS: AF-02, BZ-07, CO-07, CS-07, FX-09, JJ-06, LA-07, OO-01, OU-16, SN-03, SQ-10, UU-05

3.6.2.1 Definitions

For the purposes of these Regulations:

3.6.2.1.1 Infectious substances are substances which are known or are reasonably expected to contain pathogens. Pathogens are defined as micro-organisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents such as prions, which can cause disease in humans or animals.

Note:
Toxins from plant, animal or bacterial sources which do not contain any infectious substances or toxins that are not contained in substances which are infectious substances should be considered for classification in Division 6.1 and assigned to UN 3172.

3.6.2.1.2 Biological products are those products derived from living organisms which are manufactured and distributed in accordance with the requirements of appropriate national authorities, which may have special licensing requirements, and are used either for prevention, treatment, or diagnosis of disease in humans or animals, or for development, experimental or investigational purposes related thereto. They include, but are not limited to, finished or unfinished products such as vaccines.

3.6.2.1.3 Cultures are the result of a process by which pathogens are intentionally propagated. This definition does not include patient specimens as defined below in 3.6.2.1.4.

3.6.2.1.4 Patient specimens are those collected directly from humans or animals, including, but not limited to, excreta, secreta, blood and its components, tissue and tissue fluid swabs, and body parts being transported for purposes such as research, diagnosis, investigational activities, disease treatment and prevention.

3.6.2.1.5 Medical or clinical wastes are wastes derived from the medical treatment of animals or humans or from bio-research.

3.6.2.2 Classification of Infectious Substances

3.6.2.2.1 Infectious substances must be classified in Division 6.2 and assigned to UN 2814, UN 2900, UN 3291 or UN 3373, as appropriate.

3.6.2.2.2 Infectious substances are divided into the following categories:

3.6.2.2.2.1 Category A: An infectious substance which is transported in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Indicative examples of substances that meet these criteria are given in Table 3.6.D.

Note:
An exposure occurs when an infectious substance is released outside of the protective packaging, resulting in physical contact with humans or animals.

(a) Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

(b) Assignment to UN 2814 or UN 2900 must be based on the known medical history and symptoms of the source human or animal, endemic local conditions, or professional judgement concerning individual circumstances of the source human or animal.

Notes:

1. *The proper shipping name for UN 2814 is **Infectious substance, affecting humans**. The proper shipping name for UN 2900 is **Infectious substance, affecting animals** only.*
2. *The following table is not exhaustive. Infectious substances, including new or emerging pathogens, which do not appear in the table but which meet the same criteria must be assigned to Category A. In addition, if there is doubt as to whether or not a substance meets the criteria it must be included in Category A.*
3. *In the following table, the micro-organisms written in italics are bacteria, mycoplasma, rickettsia or fungi.*

TABLE 3.6.D
Indicative Examples of Infectious Substances Included in Category A in Any Form Unless Otherwise Indicated (3.6.2.2.2.1)

UN Number and Proper Shipping Name	Micro-organism
UN 2814 Infectious substance affecting humans	*Bacillus anthracis* (cultures only) *Brucella abortus* (cultures only) *Brucella melitensis* (cultures only) *Brucella suis* (cultures only) *Burkholderia mallei* – *Pseudomonas mallei* – Glanders (cultures only) *Burkholderia pseudomallei* – *Pseudomonas pseudomallei* (cultures only) *Chlamydia psittaci* – avian strains (cultures only) *Clostridium botulinum* (cultures only) *Coccidioides immitis* (cultures only) *Coxiella burnetii* (cultures only) Crimean-Congo hemorrhagic fever virus Dengue virus (cultures only) Eastern equine encephalitis virus (cultures only) *Escherichia coli*, verotoxigenic (cultures only) Ebola virus Flexal virus *Francisella tularensis* (cultures only) Guanarito virus Hantaan virus Hantavirus causing hemorrhagic fever with renal syndrome Hendra virus Hepatitis B virus (cultures only) Herpes B virus (cultures only) Human immunodeficiency virus (cultures only) Highly pathogenic avian influenza virus (cultures only) Japanese Encephalitis virus (cultures only) Junin virus Kyasanur Forest disease virus Lassa virus Machupo virus Marburg virus Monkeypox virus *Mycobacterium tuberculosis* (cultures only) Nipah virus Omsk hemorrhagic fever virus *Poliovirus* (cultures only) Rabies virus (cultures only) *Rickettsia prowazekii* (cultures only) *Rickettsia rickettsii* (cultures only) Rift Valley fever virus (cultures only) *Russian spring-summer encephalitis virus* (cultures only)

TABLE 3.6.D
Indicative Examples of Infectious Substances Included in Category A in Any Form Unless Otherwise Indicated (3.6.2.2.2.1) *(continued)*

UN Number and Proper Shipping Name	Micro-organism
	Sabia virus
	Shigella dysenteriae type 1 (cultures only)
	Tick-borne encephalitis virus (cultures only)
	Variola virus
	Venezuelan equine encephalitis virus (cultures only)
	West Nile virus (cultures only)
	Yellow fever virus (cultures only)
	Yersinia pestis (cultures only)
UN 2900 Infectious substances affecting animals	African swine fever virus (cultures only)
	Avian paramyxovirus Type 1 – Velogenic Newcastle disease virus (cultures only)
	Classical swine fever virus (cultures only)
	Foot and mouth disease virus (cultures only)
	Lumpy skin disease virus (cultures only)
	Mycoplasma mycoides – Contagious bovine pleuropneumonia (cultures only)
	Peste des petits ruminants virus (cultures only)
	Rinderpest virus (cultures only)
	Sheep-pox virus (cultures only)
	Goatpox virus (cultures only)
	Swine vesicular disease virus (cultures only)
	Vesicular stomatitis virus (cultures only)

3.6.2.2.2.2 Category B: An infectious substance which does not meet the criteria for inclusion in Category A. Infectious substances in Category B must be assigned to UN 3373.

Note:
The proper shipping name of UN 3373 is ***Biological substance Category B****.*

3.6.2.2.3 Exceptions

3.6.2.2.3.1 Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

3.6.2.2.3.2 Substances containing micro-organisms, which are non-pathogenic to humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

3.6.2.2.3.3 Substances in a form that any present pathogens have been neutralized or inactivated such that they no longer pose a health risk are not subject to these Regulations unless they meet the criteria for inclusion in another class.

3.6.2.2.3.4 Environmental samples (including food and water samples), which are not considered to pose a significant risk of infection are not subject to these Regulations, unless they meet the criteria for inclusion in another class.

3.6.2.2.3.5 Dried blood spots, collected by applying a drop of blood onto absorbent material, or faecal occult blood screening tests and blood or blood components which have been collected for the purposes of transfusion or for the preparation of blood products to be used for transfusion or transplantation and any tissues or organs intended for use in transplantation are not subject to these Regulations.

3.6.2.2.3.6 Patient specimens for which there is minimal likelihood that pathogens are present are not subject to these Regulations if the specimen is packed in a packaging which will prevent any leakage and which is marked with the words “Exempt human specimen” or “Exempt animal specimen,” as appropriate. The packaging must meet the following conditions:

(a) The packaging must consist of three components:

1. a leak-proof primary receptacle(s);

2. a leak-proof secondary packaging; and

3. an outer packaging of adequate strength for its capacity, mass and intended use, and with at least one surface having minimum dimensions of 100 mm × 100 mm;

(b) For liquids, absorbent material in sufficient quantity to absorb the entire contents must be placed between the primary receptacle(s) and the secondary packaging so that, during transport, any release or leak of a liquid substance will not reach the outer packaging

and will not compromise the integrity of the cushioning material;

(c) When multiple fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated to prevent contact between them.

Note:
In determining whether a patient specimen has a minimal likelihood that pathogens are present, an element of professional judgment is required to determine if a substance is exempt under this paragraph. That judgment should be based on the known medical history, symptoms and individual circumstances of the source, human or animal, and endemic local conditions. Examples of specimens which may be transported under this paragraph include the blood or urine tests to monitor cholesterol levels, blood glucose levels, hormone levels, or prostate specific antigens (PSA); tests required to monitor organ function such as heart, liver or kidney function for humans or animals with non-infectious diseases, or therapeutic drug monitoring; tests conducted for insurance or employment purposes and are intended to determine the presence of drugs or alcohol; pregnancy tests; biopsies to detect cancer; and antibody detection in humans or animals in the absence of any concern for infection (e.g. evaluation of vaccine induced immunity, diagnosis of autoimmune disease, etc.).

3.6.2.3 Biological Products

3.6.2.3.1 For the purposes of these Regulations, biological products are divided into the following groups:

(a) those which are manufactured and packaged in accordance with the requirements of appropriate national authorities and transported for the purposes of final packaging or distribution, and use for personal health care by medical professionals or individuals. Substances in this group are not subject to these Regulations;

(b) those which do not fall under paragraph (a) and are known or reasonably believed to contain infectious substances and which meet the criteria for inclusion in Category A or Category B. Substances in this group must be assigned to UN 2814, UN 2900 or UN 3373, as appropriate.

Note:
Some licensed biological products may present a biohazard only in certain parts of the world. In that case, competent authorities may require these biological products to be in compliance with local requirements for infectious substances or may impose other restrictions.

3.6.2.4 Genetically Modified Micro-organisms and Organisms

3.2.6.2.4.1 Genetically modified micro-organisms not meeting the definition of an infectious substance must be classified according to Subsection 3.9.

3.6.2.5 Medical or Clinical Wastes

3.6.2.5.1 Medical or clinical wastes containing Category A infectious substances must be assigned to UN 2814 or UN 2900, as appropriate. Medical or clinical wastes containing infectious substances in Category B, must be assigned to UN 3291. For the assignment, international, regional or national waste catalogues may be taken into account.

3.6.2.5.2 Medical or clinical wastes which are reasonably believed to have a low probability of containing infectious substances must be assigned to UN 3291.

Note:
The proper shipping name for UN 3291 is ***Biomedical waste, n.o.s., Clinical waste, unspecified, n.o.s.*** *or* ***Medical waste, n.o.s.*** *or* ***Regulated medical waste, n.o.s.***

3.6.2.5.3 Decontaminated medical or clinical wastes which previously contained infectious substances are not subject to these Regulations unless they meet the criteria for inclusion in another class.

3.6.2.6 Infected Animals

3.6.2.6.1 A live animal that has been intentionally infected and is known or suspected to contain an infectious substance must not be transported by air unless the infectious substance contained cannot be consigned by any other means. Infected animals may only be transported under terms and conditions approved by the appropriate national authority.

3.6.2.6.2 Unless an infectious substance cannot be consigned by any other means, live animals must not be used to consign such a substance.

3.6.2.6.3 Animal material affected by pathogens of category A or which would be assigned to category A in cultures only, must be assigned to UN 2814 or UN 2900 as appropriate.

3.6.2.7 Patient Specimens

Patient specimens must be assigned to UN 2814, UN 2900 or UN 3373 as appropriate except if they comply with 3.6.2.2.3.

3.7 Class 7 — Radioactive Material

STATE VARIATIONS: RUG-01, USG-10

3.7.1 Definition

Radioactive material means any material containing radionuclides where both the activity concentration and the total activity in the consignment exceed the values specified in 10.3.2.

The following radioactive materials are not included in Class 7 for the purposes of these Regulations:

(a) Radioactive material implanted or incorporated into a person or live animal for diagnosis or treatment;

(b) Radioactive material in consumer products which have received regulatory approval, following their sale to the end user;

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

UCSF and SAN FRANCISCO GENERAL HOSPITAL
Manual of Operations- Blood Draws

MITCHELL COHEN, MD, FACS
UCSF- DEPARTMENT OF SURGERY- SFGH

Sponsored by National Heart Lung and Blood Institute (NHLBI),
and the National Institutes for Health (NIH)

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

UT HEALTH HOUSTON
Manual of Operations- Blood Draws

NENA MATIJEVIC, PharmD, PhD
UT HEALTH - DEPARTMENT OF SURGERY– CENTER FOR TRANSLATIONAL INJURY RESEARCH

Sponsored by National Heart Lung and Blood Institute (NHLBI),
and the National Institutes for Health (NIH)

Identifying patients

- **Initial Blood draw occurs for <u>all</u> Highest Trauma Activation with no obvious exclusion (pregnant, prisoner, pediatric)**

- Initial blood samples will be drawn as soon as possible in the Emergency Department on all patients admitted under the highest level of trauma activation.
- Every attempt should be made to collect the blood sample before significant resuscitation takes place.
- All patients arriving to the ED with the highest level of trauma activation will be noted on the screening log.

The Sample Tubes

Samples to be obtained at Initial Draw and follow up (if randomized):

- 1 x 2.7 ml Blue top citrated tube for functional assays (TEG and Multiplate)
- 2 x 4.5ml Blue top citrated tube for coagulation assays
- 1 x 4.5ml Blue top citrated tube with benzamidine
- 1 x 5 ml Lavender/grey Cyto-Chex BCT with preservative for flow cytometry

Initial Blood Draw

- Blood will be drawn only by clinical nurse or ED staff
- Stay out the way of the ED team, but maintain presence in the Trauma room, and remind the nurse of the need for the PROPPR blood draw, if necessary
- This blood sample is a huge NIH focus of PROPPR.
- Record all fluids, vitals, ABG scores, drugs given, etc. (PROPPR CRF)

Obtaining Blood Samples

Five (5) tubes of blood are drawn, for a total of 23 ml of blood for EVERY sample

- Prepare the tubes, specimen requisition form (NON PROPPR site specific), labels, etc. needed for the specimen collection process.

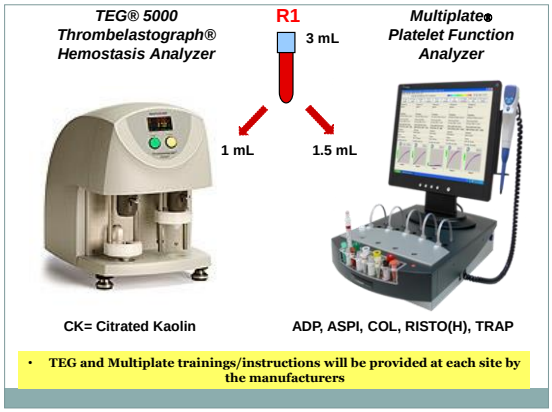
<u>The sequential order of draw should be:</u>

(R1) 2.7mL blue top
(R2) 4.5mL blue top
(R3) 4.5mL blue top
(R4) 4.5mL blue top with benzamidine
(R5) 5 mL lavender/grey top Cyto-Chex BCT tube

- Tubes are to be numbered (R1, R2, R3, R4, and R5) to assist the clinical staff in prioritizing the collection of the samples. The lavender/grey Cyto-Chex BCT sample tubes contain a strong anticoagulant (EDTA). **It is important to make every effort to follow the correct order of draw to prevent contamination of samples.**

(R1) 3mL blue top

- Process immediately per protocols for TEG and Multiplate for (see **SOP: TEG and Multiplate**)
- Maintain samples at room temperature (18-22 ˚ C) throughout processing.
  - **NOTE: <u>Only</u> Patients with an ABC score ≥ 2 will have the Initial Blood Draw TEG and Multiplate processed/run. All randomized patients will have have TEG and Multiplate run, regardless of ABC score.**
  - **NOTE: TEG/Multiplate should not wait for PROPPR randomization determination (completion of FORM 1). All TEG/Multiplate samples should be processed immediately upon ABC score ≥ 2 or randomization of PROPPR.**
  - **NOTE: Non-randomized patients with ABC score <2 should not have TEG/Multiplate processed but should have plasma and whole blood BCT tube processed.**



- **TEG and Multiplate trainings/instructions will be provided at each site by the manufacturers**

(R2,R3,R4) 3 Blue top 4.5 mL tubes

<u>COMPLETED BY THE CLINICAL LAB or equivalent or per local site protocol:</u>

2 x 4.5ml Blue top citrated tube for coagulation assays

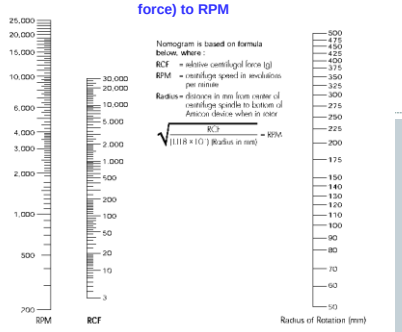
1 x 4.5ml Blue top citrated tube with benzamidine

- Maintain sample at room temperature (18-22 ˚ C) throughout processing.

- Centrifuge the sample at **2500xg for 20 min**, at room temperature. This causes separation of the sample into 3 distinct phases: the upper layer is the platelet-free plasma (contains clotting factors), the narrow middle layer is the 'buffy coat' (white blood cells), and the bottom layer is the red blood cells

NOTE: Use only centrifuge with swing bucket rotor. If you have to convert maximum relative centrifugal force (RCF) to RPM: Determine centrifuge 's radius of rotation (in mm) by measuring distance from center of centrifuge spindle to bottom of device when inserted into rotor. Lay a ruler or draw a line from radius value in right-hand column value that corresponds to the device 's maximum rated g-force. Then read the maximum value from column at left.

Nomogram for converting maximum relative centrifugal force (RCF, i.e., g-force) to RPM



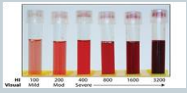
To convert maximum relative centrifugal force (RCF) to RPM: Determine centrifuge 's radius of rotation (in mm) by measuring distance from center of centrifuge spindle to bottom of device when inserted into rotor. Lay a ruler or draw a line from radius value in right-hand column value that corresponds to the device 's maximum rated g-force. Then read the maximum value from column at left.

(R2,R3,R4) 3 Blue top 4.5 mL tubes (cont.)

- Following centrifugation, the plasma should be aliquoted into the appropriate cryovials 1 per tube and immediately frozen at -80°C and stored at the site until shipped to the Core Lab in Houston (monthly).
- Once tubes are spun and aliquotted they will be labeled using pre-printed PROPPR labels. Label the aliquot cryovials (**3 cryovials per patient per time point for enrolled/randomized patients, or 4 cryovials for eligible but not randomized patients, initial blood draw only**) with the ID labels associated with the parent tubes and place the cryovials in a rack.

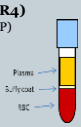
Hemolysis and Buffy Coat

- After the centrifuge has stopped, remove and inspect the specimens for hemolysis. If the plasma is either red tinged or pink, the blood sample is hemolyzed. **Document the level of hemolysis in the Blood Collection form.** Grade the hemolysis from Slight Hemolysis, Moderate Hemolysis to Marked Hemolysis (Hemolysis grading chart). **Do not discard the sample**.



- **Aliquot plasma from each of the 3 tubes (R2, R3, and R4) into a 3 ml screw-cap color coded cryovials** (R2CP, R3CP, R4BP)

  <u>Note</u>: When removing plasma after centrifugation do not disturb the white blood cells layer, called the buffy coat, which forms a thin layer between the upper plasma layer and the lower layer of packed red blood cells. It is critical that only the clear plasma be aspirated when preparing these sample aliquots. ***Remove only 3/4 of the plasma volume above the buffy coat, and leave the rest (1/4) in the tube.***



(R5) 5 mL Lavender/grey Cyto-Chex BCT

COMPLETED BY THE RESEARCH STAFF:

INITIAL BLOOD DRAW: Cyto-Chex BCT Lavender/grey top tube *for Randomized PROPPR patients*

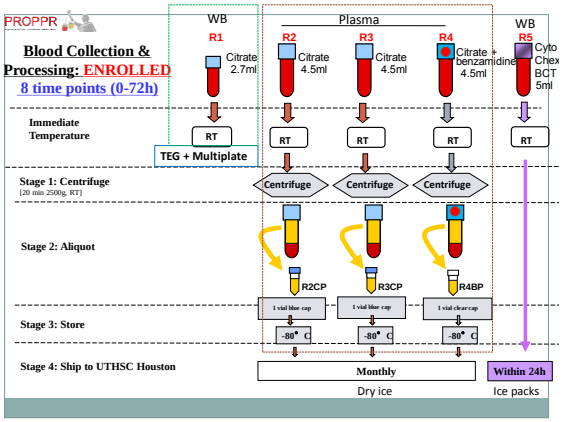
- Immediately after collection, gently invert the tube 10 times, **DO NOT SHAKE.** Leave it at room temperature until ready to ship to UT Houston Core Lab. The Cyto-Chex BCT tubes must be shipped **within 24 hours** via overnight courier to the UT Houston Core Laboratory.

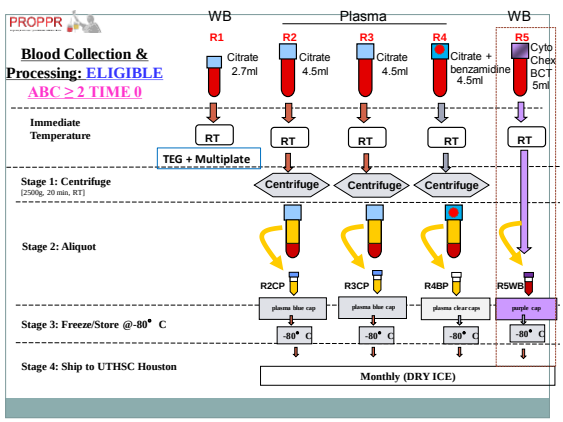
- **NOTE:** If a participant's blood draw yields less than the required number of tubes, collected samples still need to be processed and sent to the Houston Core Lab.

(R5) 4.5 mL Lavender/grey Cyto-Chex BCT

INITIAL BLOOD DRAW: Cyto-Chex BCT Lavender/grey top tube *for ELIGIBLE BUT NOT RANDOMIZED SUBJECTS:*

- Gently mix/re-suspend the blood by inverting the tube 10 times. **DO NOT SHAKE.**
  - Label 1 purple top cryovial with the Lab Sample ID labels associated with the parent tubes and place the vials in a rack.
  - Transfer the blood to pre-labeled purple top cryovials using the graduated transfer pipet: R5WB blood (Purple top cryovial)
  - After creating the aliquots, place the cryovials in the upright position into appropriate boxes and store them at -80° C until shipping to Houston Central lab.
- **NOTE: Please make sure that all cryovials have a study label on them. Make sure the label is securely attached to the cryotube. Fasten the caps onto these vials.**
- **NOTE: Eligible but non-randomized patients should have CytoChex BCT tube aliquoted and frozen without centrifugation. Non-randomized patients will not have daily shipping of Cyto-Chex BCT tubes but frozen tubes will be batch shipped with frozen plasma (see the instructions below)**
- ***Specimens must be placed in the -80° degree C freezer in the upright position (freezer box with dividers) as soon as possible but no later than 60 minutes from the collection time. Record the date and time of freezing samples on the form*** *(PROPPR Biospecimen Collection Form).*





Labeling Sample Tubes

Each site will receive two batches of labels:

- Initial Draw Only (100 sets)
- Randomized PROPPR Patient (50 sets)

- All sample tubes will begin with local site-specific labels (MR#, Trauma name, date and time) and given to Clinical Lab for processing and aliquoting
- Once disposition of patient is known, Coordinator will affix the correct labels to initial draw tubes (and sequential draw tubes if applicable).

PROPPR Randomized Patient

Patient is Randomized:

- Coordinator affixes **PROPPR randomized** patient labels to CRF and to all initial draw tubes and aliquots
- Assure that screening ID and Randomization ID numbers are visible
- Corresponding draw PROPPR randomized patient labels affixed after each draw has been processed and aliquoted by Clinical Lab.

Patient is Initial Draw Only, ≥2 ABC score

Patient is eligible, but not Randomized:

- Coordinator runs TEG and Multiplate test on 2.7mL tube
- After patient deemed **PROPPR initial draw only**, affix corresponding labels to CRF and to all initial draw tubes and aliquots
- Assure that screening ID and Randomization ID numbers are visible
- Samples frozen and batch shipped to Houston monthly

Patient is Initial Draw Only, <2 ABC score

- **NO TEG/Multiplate**, but should have plasma and whole blood BCT tube processed.
- Affix **PROPPR initial draw only** and corresponding labels to CRF and to all initial draw tubes and aliquots
- Assure that screening ID and Randomization ID numbers are visible
- Samples frozen and batch shipped to Houston monthly

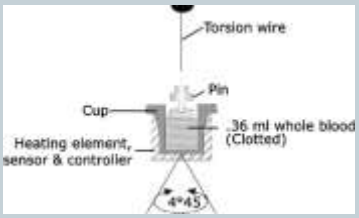
PROPPR

UCSF and SAN FRANCISCO GENERAL HOSPITAL
Manual of Operations- TEG Testing

MITCHELL COHEN, MD, FACS
UCSF- DEPARTMENT OF SURGERY- SFGH

Sponsored by National Heart Lung and Blood Institute (NHLBI),
and the National Institutes for Health (NIH)

The TEG Machine



TEG Materials

- **MATERIALS, REAGENTS AND EQUIPMENT:**
  - TEG Machine
  - Tabletop centrifuge
  - Refrigerator/freezer
  - TEG Kaolin reagent (purple label, located in your refrigerator)
  - Pins/Cups (as one unit)
  - Pipette tips (will need 2 sizes, 1000uL and 20uL)
  - Small plastic container to dispose of contaminated pipette tips in-between test steps
  - Protective equipment (gloves, eye protection)

Supplies: Pipettes & tips

Supplies: Centrifuge & sharps container

Supplies: TEG cups & pins

Reagents

PRE-TEST REAGENT PREPARATION

Kaolin

- Remove from refrigerator just before use.
- Spin down in small tabletop centrifuge for a few seconds before use.

CaCl2

- Found in the Level I/II Control boxes in the refrigerator
- Store at room temperature once opened
- If out, prepare CaCl2 solution on benchtop:
  - **Solution:** 0.2M CaCl2 in NaCl
  - Add 200uL of 1M CaCl2 solution to 800uL of normal saline (NS)
  - Mix by pipetting.
  - Store at room temperature.

Test Preparation

Supplies, Machine and Subject ID/ Test ID Entry

- Reagents must be kept in the refrigerator.
- Check the bubble level on top of the TEG machine:
  - If machine is not level, use the adjustable legs on bottom of machine to straighten until bubble is in center of target
- If a pop up comes up asking to run a QC test – hit skip (QC test should be run once a week)
- To run a test, click the 'TEG' icon located in upper right side of the toolbar.
- The screen will show the 4 channels with drop-down menus for test, patient ID, and sample ID for each channel (you will usually use channels 1 and 2)
  - Test Name: Go to the drop down menu on the left that shows " ---N- Test"
    - 1st channel: CK – citrated kaolin TEG
  - Patient ID:
    - To select subject ID number and hour, go to top drop down box on top right;
    - Existing patient: select from the drop-down menu;
    - New Patient: type in "# "ex: [1507]
    - If New Patient, answer "Yes" to pop-up "Is this a new patient?";
      - Enter Trauma Name for "Patient ID" (ex. [Tr. Oscar]). Then hit done.
- In the bottom right box of channel fields, select **hour of draw from drop-down menu (ex: [oh])**

Cup and Pin Set-up

- The cup/pin lever should already be in the load position
  - This is the way the machine should be left after a test.
- Slide white platform down until you hear a click, but **NOT** all the way down to the base of the machine.
  - **If pushed all the way down, it will prevent the cup from loading properly**.

Cup and Pin Set-up

- Place cup/ pin into the platform slot.

Cup and Pin Set-up

- Place cup/ pin into the platform slot.
- While **HOLDING ONTO the top of machine** so it doesn' t knock over, **slide the white platform with cup/pin up into black loading cylinder** on machine.
- Once the platform is all the way up, **press the white button** on the base of the platform **3 TIMES** to secure the pin.

Cup and Pin Set-up

- Place cup/ pin into the platform slot.
- While **HOLDING ONTO the top of machine** so it doesn' t knock over, **slide the white platform with cup/pin up into black loading cylinder** on machine.
- Once the platform is all the way up, **press the white button** on the base of the platform **3 TIMES** to secure the pin.
- Once pin is in place, pull the platform back down **about halfway, and NOT all the way to the bottom.**

Cup and Pin Set-up

- Once pin is in place, pull the platform back down **about halfway, and NOT all the way to the bottom.**
- Hold the bottom of platform with two fingers, and push down on the rim of the cup with your thumbs to securely seat the cup.
  - **Don't push platform all the way down** or you won't be able to properly seat the cup.

Cup and Pin Set-up

- Once pin is in place, pull the platform back down **about halfway, and NOT all the way to the bottom.**
- Hold the bottom of platform with two fingers, and push down on the rim of the cup with your thumbs to securely seat the cup.
  - **Don't push platform all the way down** or you won't be able to properly seat the cup.
- Check that the cup is firmly seated.

Kaolin TEG test (Mix)

Kaolin Test

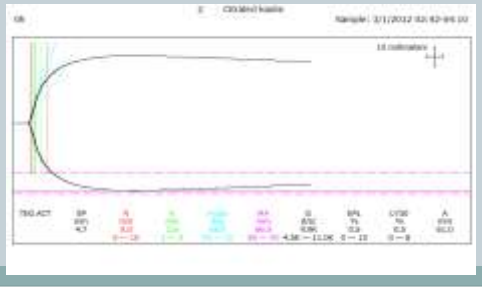
- To start Kaolin test, click on the patient study ID for the next channel to highlight and activate the channel.
- Take Kaolin tube out of fridge and spin for a few seconds in tabletop centrifuge
- Set pipette to 20uL and **pipette 20uL of CaCl2 (red top) into cup**
- Set pipette to 1mL.
- **Pipette 1mL of blood into Kaolin vial (purple top).**
- Mix 5 times by **gently inverting** purple tube.
  - **DO NOT mix by pipette**.

Kaolin TEG test (Mix and test)

- Set pipette to 340uL.
- **Pipette 340uL of Kaolin + blood mixture (purple top) into the cup**.
  - **DO NOT mix by pipetting**; extra mixing with Kaolin will cause unwanted contact activation.
- Slide the cup up and into position.
- Move the silver lever over to "test" position,
- Confirm the correct channel is highlighted as active on t screen.
  - If unsure, click within one of the channel fields where the subject data is entered. This will activate this channel as the primary channel for the current test.
- Hit start by pressing the green icon at top of screen.
- Test will run for about 1 ½ hrs and stop on its own.

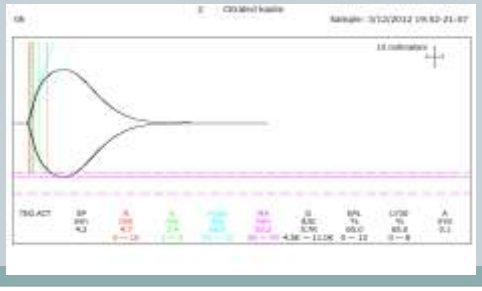
Sample good tracings

- Normal kaolin TEG



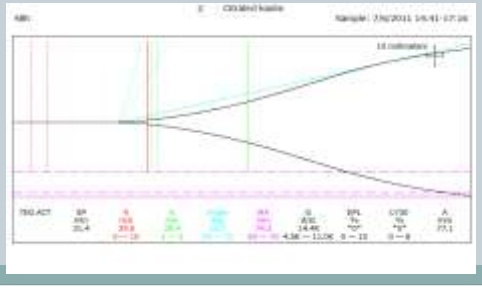
Sample good tracings

- Hyperfibrinolysis



Sample good tracings

- Impaired coagulation in a patient on heparin

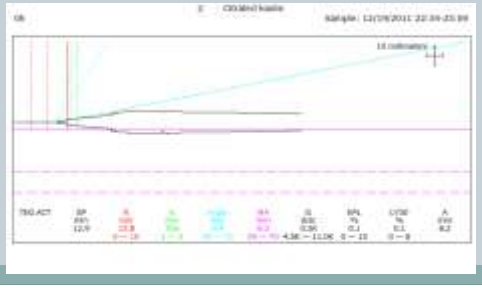


Sample tracings

- Lines should always look smooth
- No sudden changes or sharp edges
- Long clotting times and flat lines may be appropriate if a patient is receiving anticoagulants like heparin, but may be a technical problem if the patient is not
- TEG machine may detect problems with cup and pin seating and give an "**eTest/Disposable error**"
- …Repeat these tests if any doubt.

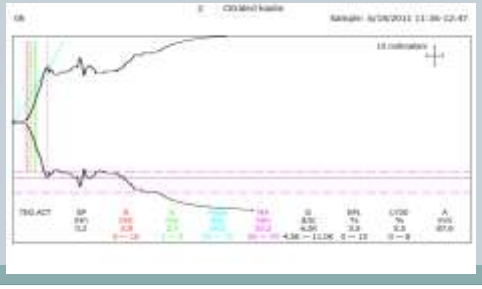
Sample *bad* tracings

- Cup/pin incorrectly seated



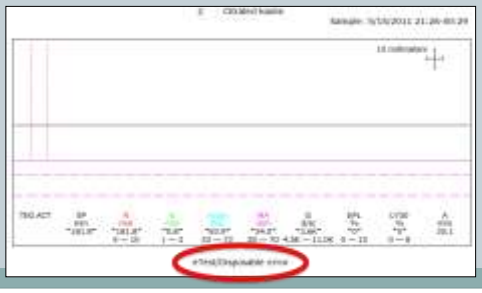
Sample *bad* tracings

- Cup/pin incorrectly seated



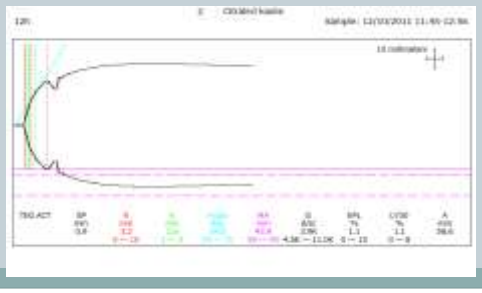
Sample *bad* tracings

- Cup/pin incorrectly seated; "eTest/Disposable error"



Sample *bad* tracings

- TEG machine bumped during test



Kaolin TEG test (Recording & clean up)

- Once tests are finished, go to tracing review screen by clicking on "Done" from TEG channel setup screen; to view each tracing, double-click it; to return to tracing review screen, double-click the tracing.
- While in full-screen tracing view mode, click "Print" in upper left
- Sign and date results- Enter results into PROPPR online database- *Openclinica*. **SOP- Lab Data Entry Procedures** for data entry protocol.
- To eject cup/pin move silver lever to "load" position. Push lever down and this will eject the cup & pin together. Push the white platform all the way down past the first click to the base of the machine; this will push up on the bottom of the cup to eject it.
- **Put used cups/pins/pipette tips in biohazard waste bin**
- Leave platform up and lever in load position when TEG not in use

PROPPR

Pragmatic, Randomized Optimal Platelet and Plasma Ratios

TEG and Multiplate Raw Data Extraction Webinar

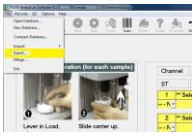
June 26, 2013

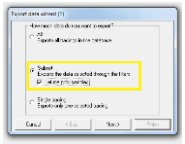
MITCHELL COHEN, MD, FACS
UCSF- DEPARTMENT OF SURGERY- SFGH

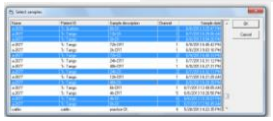
TEG Raw Data Extraction Overview

- Open TEG by double clicking on the TEG icon on your desktop, login as requested.
- Open the TEG database that contains the patient data of interest.
- Select all PROPPR tests for a specific patient and export the data into: one CRD file and one VEL file. Resave these files in excel.
- Rename exported CRD and VEL files "PROPPR STUDY ID", ex: "**PROPPR_1210100**"
- End product: You will have two excel files per patient that contain all time points of test results.
- Refer to: "PROPPR SOP for TEG Raw Data Extraction_Final"

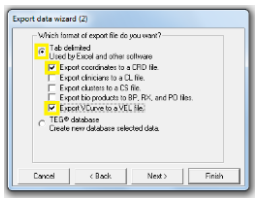
1. Open the TEG database of Interest
2. From the File option on the Main menu (top left corner), select "Export".
3. Select subset, and click "let me pick samples".
4. It will prompt you to select the tests of interest from each specific patient.
5. Click anywhere in the row to highlight the sample for a specific patient.
6. To select additional samples, hold down the Ctrl key while you select each additional test (ex: 0h, 2h, 4h etc).

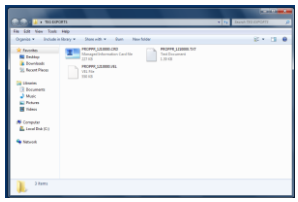




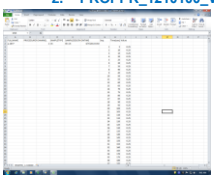


1. The next screen you will see is: "Export data wizard (2)"
2. Select "Tab delimited" and then click "Export coordinates to a CRD file" and "Export VCurve to a VEL file". Then click "Next".
3. The final screen prompts you for a filename for the export file. Type the filename of your export file into the File name field, and click Save. (Ex: "**PROPPR_1210100**"). When naming, use the primary study ID (not the lab ID or randomized ID).
4. After naming and saving the data, three files are created: a text file (.txt), a CRD file (.crd), and a VEL (.VEL) file. All three files will be saved in the same location as specified in the final screen where you named your file.

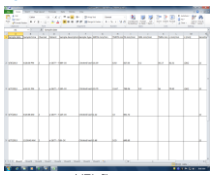




1. Open Excel, then open the CRD and VEL files to confirm that the appropriate patient tests were exported. Now save the files again as an Excel files.
2. When exporting more than one test at a time, the resulting CRD file will be one very long list of numbers with minimal breaks between tests. There will be a horizontal line with identifying test information between each test.
3. Each VEL file will have 9 spreadsheets (tabs) per patient who had all 8 time points results (one spreadsheet for each time point, plus one with calculated V-curve parameters and graphs)
4. In the end, each patient should have two excel files that contain all raw data for each TEG Kaolin test at each time point.
    1. **"PROPPR_1210100_CRD.xls"**
    2. **"PROPPR_1210100_VEL.xls"**



CRD file

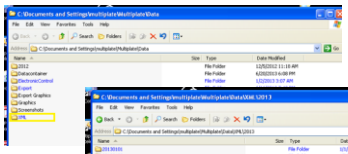


VEL file

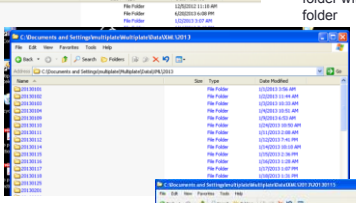
Multiplate Raw Data Extraction Overview

- Measurement data is automatically saved in both graphic and XML data files.
- Copy files of interest from Multiplate XML folder to a thumb drive.
- Rename data files for each patient at each time point for each specific test (ADP/TRAP/COL/ASPI/RISTO), transfer files into a Master excel file containing data from all tests at a certain time point.
- Refer to: "PROPPR SOP for Multiplate Raw Data Extraction_Final.doc"

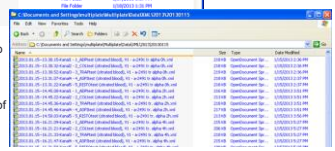
Navigating the Multiplate Data Folder



1. Open the "Data" folder on the desktop
2. Then open the "XML" folder within the Data folder



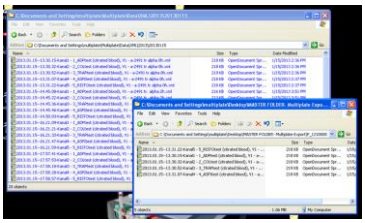
3. Tests are organized first by year and then by the day that the test was run:



4. Find the set of tests that correspond to the applicable blood sample and patient.
5. At each time point, a patient will have the following 5 separate files for each of the agonist tests: ADPtest, RISTOtest, TRAPtest, ASPItest, COLtest.

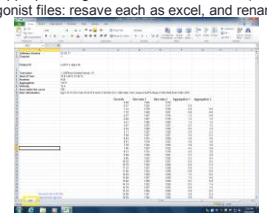
Exporting from Data Folder

1. Highlight and copy the desired files
2. Create a master folder on the desktop of the Multiplate machine for the new exported excel files. Within the master folder, create new folders for each PROPPR patient ID.
3. Paste the copied files in the PROPPR patient folder.
4. Copy the folder with exported XML test files onto the hard drive using a thumb drive.



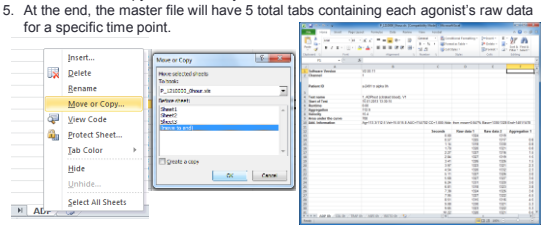
Data Organization

1. Create a new master excel file, and save as PROPPR StudyID_Timepoint (ex: "**P-1210100_0hour**"). Save as a Microsoft Excel 97/2000/XP (.xls). Please follow this naming format exactly so that files that can be easily sorted in the future
2. Each patient will have 5 files per time point, one for each agonist. You will be transferring each file to the master excel file you created, copying each agonist's data onto a new tab within the master excel file.
3. To begin, open one agonist file with Excel. Save as Microsoft Excel 97/2000/XP (.xls) in a PROPPR ID # folder. Go down to bottom tab, double click to rename from "Multiplate" to the appropriate agonist test name and time (ex: **ADP0h**). Repeat for the remaining 4 agonist files: resave each as excel, and rename tab with the agonist name.



Transferring Agonist Files into the Master File

1. Open both master file (ex: **"P-1210100_0hour.xls"**) and one agonist file to be transferred.
2. In the agonist file, Right click the tab you renamed with the agonist, click "move/copy". Click on "to document", and select your master file. Click "move to end position", then click "ok".
3. Maximize the master file, and you will see the agonist data under the new tab.
4. Repeat this process for each agonist: open the next file, right click on the renamed tab, and move/copy to the end of your master file.
5. At the end, the master file will have 5 total tabs containing each agonist's raw data for a specific time point.

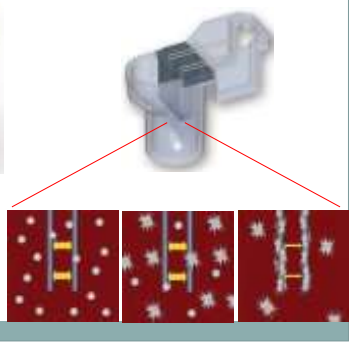


PROPPR

UCSF and SAN FRANCISCO GENERAL HOSPITAL
Manual of Operations- Multiplate Testing

MITCHELL COHEN, MD, FACS

Sponsored by National Heart Lung and Blood Institute (NHLBI),
and the National Institutes for Health (NIH)



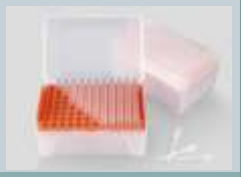
Multiplate Materials

MATERIALS, REAGENTS AND EQUIPMENT:

- Multiplate Machine
- Refrigerator/freezer
- Test cells/Sensor cables
- Pipette tips (Specific to MULTIPLATE electronic pipet)
- Reagents- ADP, TRAP, ASPI, and RISTO
- Small plastic container to dispose of contaminated pipette tips in-between test steps
- Protective equipment (gloves, eye protection)

Supplies: Lab equipment

Supplies: Multiplate equipment



Solutions

PRE-TEST REAGENT PREPARATION

- **CaCl2 solution (3mM CaCl2 in NaCl):**
  - Order from Diapharma
  - Can also be prepared from laboratory stock solutions:
    - Add 3uL of 1M CaCl2 solution to 997uL of normal saline
    - Mix by pipetting.
  - Extra tubes of calcium solution are stored in the fridge.
  - Storage: Once opened, the solution tube can be left on the Multiplate block in the holder.
- **Saline solution (0.9% sodium chloride):**
  - Stored on the Multiplate block in a hand-labeled tube.
  - Taken from clinical IV or stock bottles,common laboratory stock, or purchased from any standard laboratory supply company.
  - Stored on the Multiplate block in 3 or 5 mL standard laboratory round-bottomed polystyrene – be sure this will fit into the warmer block. Tightly reseal after each use to avoid evaporative loss.

Reagents (cont.)

- **ADP, TRAP, ASPI, and RISTO reagents:**
  - Refrigerator contains the thawed tray of reagent aliquots and the supply of lyophilized reagents to be reconstituted as needed.
  - Check expiration date on thawed, aliquoted reagents in the fridge. If expired, toss and thaw a new one.
  - The freezer contains all aliquots of reconstituted reagent.
  - If less than 3 aliquots left in the freezer supply for a particular reagent, reconstitute a new bottle of lyophilized reagent from the refrigerator.
    - Re-suspend the lyophilized reagent in 1mL reagent-grade, ultra-pure water at room temperature and mix gently by pipetting

Reagents

- **COL reagent :**
  - Lyophilized powder is reconstituted at room temperature in 1.0mL of reagent-grade, ultra-pure water and stored in the refrigerator for up to 7 days – DO NOT FREEZE ONCE RECONSTITUTED.
  - Be sure to use a new pipet tip every time, and pipet directly out of the glass bottle; since this won't be frozen and thawed, there is no need to aliquot.
  - The expiration date is written on the top of the bottle.
  - When expired, toss and reconstitute from the fridge.

Aliquotting Reagents

Prepare 1.5mL tube aliquots of each reagent. ADP, TRAP, and RISTO reagents are stable in the refrigerator for 7 days once thawed (so aliquots accommodate 10 tests); however, the ASPI reagent is only stable for 24h once thawed (so aliquots contain only enough for 2 tests):

- For ADP / TRAP reagents: **200uL** (10 tests) per aliquot
- For RISTO reagent: **500uL** (10 tests) per aliquot
- For ASPI reagent: **42uL** (2 tests) per aliquot
- Label the top of each aliquot with the name of the reagent.
- Write your initials and date of reagent preparation on the top of the original reagent bottle.
- Place aliquots in freezer box in a row behind the labeled reagent bottle.
  - Once an aliquot is thawed for use, write the date of expiration on the top of the aliquot.

<u>Frozen reagents take ~10min to thaw</u> – BE SURE to check the amount of thawed reagent in the fridge before starting a test.

Reagents and Expiration Dates

Running Multiplate

<u>TEST PREPARATION</u>

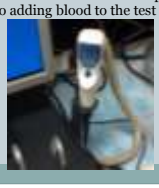
- Remove MP reagent tray from refrigerator and place on the Multiplate test platform
- Check reagent expiration dates, and equilibrate to room temperature for 10 minutes before use.
- Open and log into the Multiplate software.
- Click "F1 auto pipette" button
- Enter patient ID/sample ID together.
  - Example: [A-1460 Tr. Mike 12h]
- Click "All tests" – will copy pt ID/sample ID into all channels.
- Select the following tests – ALL **CITRATED BLOOD** –
  - Run in the exact order shown to facilitate easier data entry:
    - ADP Test (citrated blood)
    - TRAPtest (citrated blood)
    - ASPI test (citrated blood)
    - COL test (citrated blood)
    - RISTO high (citrated blood)
- Click "Start autopipette" button

Running Multiplate (cont.)

- Put new test cells into all slots. Confirm the presence of small stir bars at the bottom of each test cell. If need to open new package, <u>document date the package will expire</u> on top of package.
- **Plug sensor cable into each channel. THIS IS VERY IMPORTANT AND A COMMON THING TO FORGET.**

Running Multiplate (cont.)

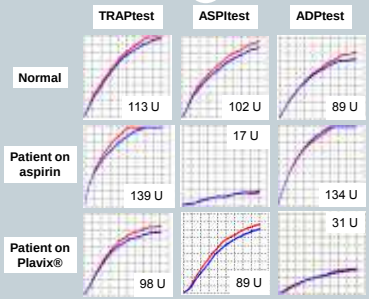
- Follow the steps shown on the computer screen:
  - Hit the large blue button on the pipette to perform the indicated step
  - **GO SLOW**; DO NOT get ahead of the automatic pipette
  - Be sure to use the appropriate diluent (saline vs. saline-CaCl2); the electronic pipettor instructions will specifically detail which is to be used for each step
  - Be sure to mix the blue-top tube of blood by **gently** inverting 3 times prior to adding blood to the test cells to ensure that the sample is well-mixed.



Good tests

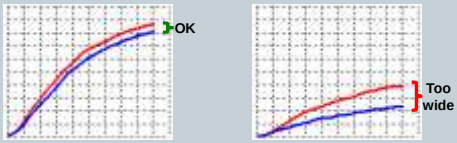
- Do not mix by pipette, as the magnetic stir bars does this for you
- **IMPORTANT**: FOR ADP, TRAP AND COL TESTS USE NORMAL SALINE WITH CALCIUM (0.9% NaCl WITH 3mM $CaCl_2$) FOR BLOOD DILUTION
- **IMPORTANT**: FOR ASPI AND RISTO TESTS USE NORMAL SALINE (0.9% NaCl) FOR BLOOD DILUTION
- **Special case to be aware of:**
  - Occasionally the pipettor malfunctions and aspirates too large a volume of reagent, producing extensive bubbles. Watch the pipettor carefully at each step; if this happens, simply click "Step back" and re-do that step.
- Tests will have an incubation period after adding blood but before adding reagents.
- When the program beeps, it is time to add the reagents as directed by the program.
- Tests are quick. You will have your result in 6 minutes.

Sample tests



Sample tests

- Duplicate lines should be close together; machine will flag results if not.
- Most tracing errors will be flagged by the machine.
- Occasionally the pipettor malfunctions and aspirates too large a volume of reagent, producing extensive bubbles. Watch the pipettor carefully at each step; if this happens, simply click "Step back" and re-do that step.
- Repeat any faulty tests.



Results and Clean-up

AFTER THE TEST

- Print results, write your initials on the hardcopy and make notes as needed.
- Enter results into PROPPR online database, *Openclinica*.
  - See **SOP- Lab Data Entry Procedures** for data entry protocol.
- File the hardcopy accordingly in Research Record Binder on the bookshelf.

CLEAN-UP AFTER TESTS COMPLETED

- Unplug all used test cells
- Return the phone cord into the 'parked' position
- **Discard of used test cells/pipette tips in the biohazard waste bin.**

Section 18.3 Instructions for Completing CRF Form # 13: Research Blood Sample Collection

Complete this form for all randomized subjects. Record research blood samples collected (if applicable). All blood sample collection time points are based on the ED arrival time (time zero), plus or minus 30 minutes. Each section corresponds to a blood sample collection time point.

Indicate if the subject died before the 2 hour blood sample was collected by checking the corresponding box at the top of the form. No additional documentation on the form is required. For all other subjects, complete each section of form #13, even if a sample time point was missed.

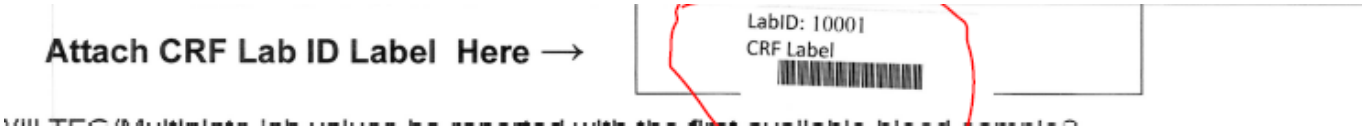
Question #1: Record the research blood sample collection date in dd/mmm/yy format.

Question #2: Record the research blood sample collection time in hh:mm format.

Question #3 Indicate if a research blood samples were collected. If a specific tube was not collected, select "no", and document the reason on form #22.
The collection tubes should be filled in the following order: 3ml blue top, one 5ml blue top, protease inhibited tube, the second 5ml blue top, and the lavender/grey ETDA tube last.

Indicate if problems occurred during research blood sample collection. If "yes", indicate the appropriate problem code from the list provided or select "other" and document on form #22. Blood sample collection problems are defined as (a.) excessive bleeding after venipuncture, (b.) loss of vacuum during collection, (c.) hematoma, (d.) Other.

Attach the lab blood tube label for the sample time point in the space provided.



Question #4: Indicate the anatomical site used for the research blood sample collection.
If "other" is selected, record the anatomical site in the space provided.

Question #5: Record the technique used to collect the sample.

Source Document: Direct observation and data entry into the CRF.

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CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 13: PROPPR Research Blood Samples

Use this form to record research blood samples collected from **randomized** subjects after the first available blood sample. **Check here** ☐ if subject **died** before the 2 hour blood sample was collected, *(form is complete, proceed to the next form)*. Provide explanation for blood samples collected outside the time window on form #22.

Section A: 2 hour Research Blood Sample

Check here ☐ if the 2 hour research blood sample was not collected *(missed).*

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			R4 Blue 4.5 mL Citrate/Benzamidine	R5 Lavender 5 mL (FLOW for CORE Lab)
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube
****Indicate if any problems occurred during collection**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**
Attach CRF Lab ID Label Here →					

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

******Research Blood Sample Collection Problem Codes: **a**= excessive bleeding after venipuncture, **b**=loss of vacuum during collection, **c**=hematoma, **d**= Other, (describe on form #22)*

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Form 13: PROPPR Research Blood Samples *(cont.)*

Section B: 4 hour Research Blood Sample

Check here ☐ if the 4 hour research blood sample was not collected *(missed).*

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			**R4 Blue 4.5 mL Citrate/Benzamidine**	**R5 Lavender 5 mL (FLOW for CORE Lab)**
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube
****Indicate if any problems occurred during collection**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**

Attach CRF Lab ID Label Here →

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

Research Blood Sample Collection Problem Codes:* ***a*= excessive bleeding after venipuncture,* ***b****=loss of vacuum during collection,* ***c****=hematoma,* ***d****= Other, (describe on form #22)*

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Form 13: PROPPR Research Blood Samples *(cont.)*

Section C: 6 hour Research Blood Sample

Check here ☐ if the 6 hour research blood sample was not collected *(missed)*.

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			**R4 Blue 4.5 mL Citrate/Benzamidine**	**R5 Lavender 5 mL (FLOW for CORE Lab)**
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube	☐ Not Collected ☐ 1/3 Tube ☐ 1/2 Tube ☐ Full Tube
****Indicate if any problems occurred during collection**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**	☐ **Yes** (check problem code) ☐ a ☐ b ☐ c ☐ d ☐ **No**
Attach CRF Lab ID Label Here →					

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

Research Blood Sample Collection Problem Codes:* ***a*= excessive bleeding after venipuncture,* ***b****=loss of vacuum during collection,* ***c****=hematoma,* ***d****= Other, (describe on form #22)*

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Form 13: PROPPR Research Blood Samples *(cont.)*

Section D: 12 hour Research Blood Sample

Check here ☐ if the 12 hour research blood sample was not collected *(missed)*.

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			**R4 Blue 4.5 mL Citrate/Benzamidine**	**R5 Lavender 5 mL (FLOW for CORE Lab)**
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube
****Indicate if any problems occurred during collection**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**
Attach CRF Lab ID Label Here →					

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

******Research Blood Sample Collection Problem Codes: **a**= excessive bleeding after venipuncture, **b**=loss of vacuum during collection, **c**=hematoma, **d**= Other, (describe on form #22)*

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Form 13: PROPPR Research Blood Samples *(cont.)*

Section E: 24 hour Research Blood Sample

Check here ☐ if the 24 hour research blood sample was not collected *(missed).*

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			**R4 Blue 4.5 mL Citrate/Benzamidine**	**R5 Lavender 5 mL (FLOW for CORE Lab)**
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube
****Indicate if any problems occurred during collection**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**
Attach CRF Lab ID Label Here →					

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

******Research Blood Sample Collection Problem Codes: **a**= excessive bleeding after venipuncture, **b**=loss of vacuum during collection, **c**=hematoma, **d**= Other, (describe on form #22)*

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CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 13: PROPPR Research Blood Samples *(cont.)*

Section F: 48 hour Research Blood Sample

Check here ☐ if the 48 hour research blood sample was not collected *(missed).*

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
(dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			**R4 Blue 4.5 mL Citrate/Benzamidine**	**R5 Lavender 5 mL (FLOW for CORE Lab)**
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube
****Indicate if any problems occurred during collection**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**
Attach CRF Lab ID Label Here →					

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

Research Blood Sample Collection Problem Codes:* ***a*= excessive bleeding after venipuncture,* ***b****=loss of vacuum during collection,* ***c****=hematoma,* ***d****= Other, (describe on form #22)*

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Study ID # ___ ___ ___ ___ ___ ___ ___ **(Bar Code)**

CONFIDENTIAL

CRF Version Date: 2012SEP05 Completed By: ___ ___ ___

Form 13: PROPPR Research Blood Samples *(cont.)*

Section G: 72 hour Research Blood Sample

Check here ☐ if the 72 hour research blood sample was not collected *(missed).*

1. Research Blood Sample Collection Date: ___ ___ / ___ ___ ___ / ___ ___
dd/mmm/yy)

2. Research Blood Sample Collection Time: ___ ___ : ___ ___
(24hr Clock in hh:mm)

3. Record the collection information in the table below.

	COAGs. *(Blue Top Sodium Citrate)*			**R4 Blue 4.5 mL Citrate/Benzamidine**	**R5 Lavender 5 mL (FLOW for CORE Lab)**
	R1 Blue 2.7 mL Tube *(Site TEG/Multiplate)*	**R2 Blue 4. 5 mL Tube**	**R3 Blue 4.5 mL Tube**		
	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube	□ Not Collected □ 1/3 Tube □ 1/2 Tube □ Full Tube
****Indicate if any problems occurred during collection**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**	□ **Yes** (check problem code) □ a □ b □ c □ d □ **No**
Attach CRF Lab ID Label Here →					

4. What site was used to collect the research blood sample? *(Select one)*

☐ Central Line ☐ Arterial Line ☐ Peripheral Vein

☐ Peripheral IV Line ☐ Other *(specify)*:_____ ☐ Unknown

5. Indicate the technique used to obtain the research blood sample.

☐ Syringe ☐ Vacutainer ☐ Unknown

******Research Blood Sample Collection Problem Codes: ***a****= excessive bleeding after venipuncture, **b**=loss of vacuum during collection, **c**=hematoma, **d**= Other, (describe on form #22)*

Section 18.4 Instructions for Completing CRF Form #14: Research Blood Sample TEG/Multiplate Results

This form is optional for screening failures and required for randomized subjects. Record research blood sample TEG and Multiplate results at the time points listed, if applicable.

Indicate if the subject died before the 2 hour blood sample was collected by checking the corresponding box at the top of the form. No additional documentation on the form is required. For all other subjects, record lab results for each TEG/Multiplate time point or indicate if the sample was missed.

Section A:
Attached lab ID labels for each lab sample time point in the corresponding spaces provided.

Sections A & B:
Record the research blood sample collection date in dd/mmm/yy format.

Record the start time (time lab analysis initiated) in hh:mm format.

Enter lab result values in the space provided.

Section C:
Indicate if wave form data was transmitted to the HDCC. Detailed procedures are listed in the LAB Moo.

Source Document: Hospital Medical Record, Lab Results, Lab Log, Direct observation and data entry into the CRF.

Use the following code for unknown data values:
NK= Unknown NR= Not Recorded/Not Done

Form 14: PROPPR Research Blood Sample TEG and Multiplate Results

Use this form to record research blood sample TEG and Multiplate results. **Check here** ☐ if the subject died before any research blood samples could be obtained. The 2 hour and beyond TEG/Multiplate tests should only be performed on **randomized** subjects.

Section A: TEG Results

Sample Time Point		Date / Start Time	*Split Point (min.)*	R-Time *(min.)*	K-Time *(min.)*	Alpha Angle (%)	Max. Amp. *(mm)*	G-Value *(d/sc)*	Ly30 (%)	Ly60 (%)	TMRTG	MRTG	TG
1st Available (Time Zero)	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
2 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
4 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
6 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
12 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
24 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
48 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.
72 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.

TEG/Multiplate Lab ID Labels

Apply 1st Available Lab ID Label Here	Apply 2 hr Lab ID Label Here	Apply 4 hr Lab ID Label Here	Apply 6 hr Lab ID Label Here
Apply 12 hr Lab ID Label Here	Apply 24 hr Lab ID Label Here	Apply 48 hr Lab ID Label Here	Apply 72 hr Lab ID Label Here

Form 14: PROPPR Research Blood Sample TEG and Multiplate Results *(cont.)*

Section B: Multiplate Results

Sample Time Point		Date / Start Time	*ADP AUC (U)*	ADP AG(AU)	*ADP VEL (AU/min)*	COL AUC (U)	COL AG (AU)	COL VEL (AU/min)	TRAP AUC (U)	TRAP AG (AU)	*TRAP VEL (AU/min)*	*ASPI AUC (U)*	ASPI AG (AU)	ASPI VEL (AU/min)	RISTO AUC (U)	RISTO AG (AU)	RISTO VEL (AU/min)
1st Ave Time Zero	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
12 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
24 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
48 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
72 hour	□ Done □ Not Done	/ / :	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Study ID # ___ ___ ___ ___ ___ ___ ___

CONFIDENTIAL **(Bar Code)**

CRF Version Date: 2012JUL25 Completed By: ___ ___ ___

Form 14: PROPPR Research Blood Sample TEG and Multiplate Results *(cont.)*

Section C: TEG/Multiplate Wave Form/Raw Data

Sample Time Point	Wave Form / Raw Data Available?	
1st Available (Time Zero)	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
2 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
4 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
6 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
12 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
24 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
48 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____
72 hour	☐ **YES** →	Date information sent to HDCC/CORE LAB: __ __ / __ __ __ / __ __
	☐ **NO** →	□ Blood Sample Not Collected □ Other: _____

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

PROPPR Lab Shipment Log:

Use this log to record research lab sample shipments to the CORE research lab. Keep one copy for your site records and include 1 copy with the lab shipment. Print a new form for each shipment. Refer to Lab MOO for packaging and shipping information.

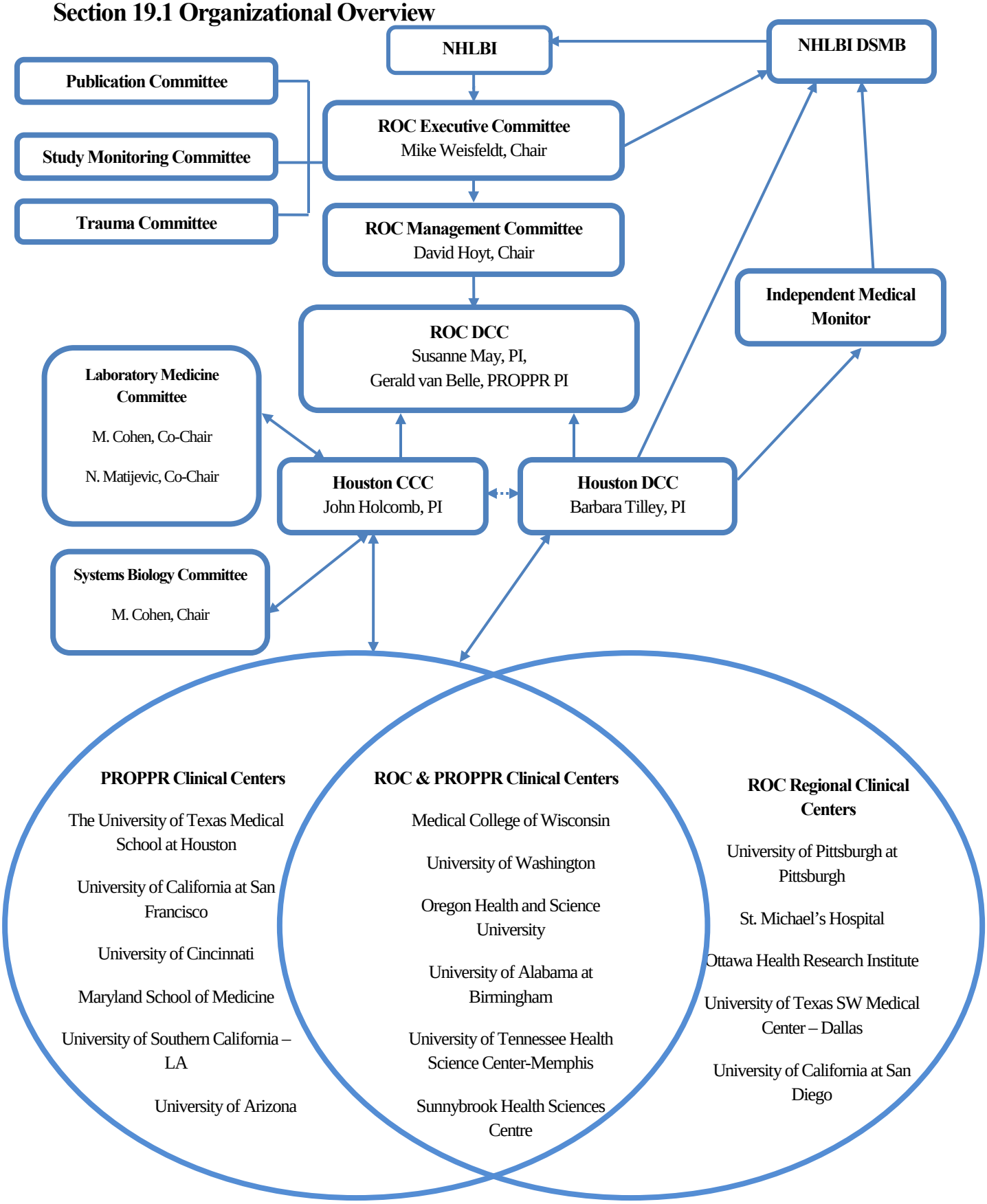
Date of Shipment: ___ / ___ / ___ Shipment Tracking Number:_____

*(**For Houston Site Only**, Record Today's Date)*

Lab Sample ID Number or Bar Code Label	Lab Sample ID Number or Bar Code Label	Lab Sample ID Number or Bar Code Label

Chapter 19 PROPPR Organizational Structure

Section 19.1 Organizational Overview



Section 19.2 Ancillary Studies – To Be Determined

Section 19.3 Publication Policies – To Be Determined

Section 19.4 Trial Time Line

PROPPR Timeline *Based on ROC fiscal year (January 1 – December 31) and budget.*					
Activities	**Period 1 10/10-12/10**	**Period 2 1/11-12/11**	**Period 3 1/12-12/12**	**Period 4 1/13-12/13**	**Period 5 1/14-9-14**
Planning	✓	✓			
Site Training		✓	✓		
IRB approval/Community Consultation		✓	✓		
Enrollment			✓	✓	✓
Follow-up to 30 days			✓	✓	✓
Trial Monitoring			✓	✓	✓
On-going Data Analysis			✓	✓	✓
Trial Close-out					✓
Sample Collection/Lab Analysis			✓	✓	✓

Appendix 1

IND# 14929

Protocol:

Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)

Table of Contents

Protocol Title: Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)

Principal Investigator:
Gerald van Belle, Ph.D.
Resuscitation Outcome Consortium (ROC) Professor
Department of Biostatistics and Environmental and Occupational Health Sciences
University of Washington
Seattle, Washington 98195-7232
Phone: 206-221-4185
vanbelle@uw.edu

Houston Clinical Coordinating Center (HCCC) Principal Investigator:
John B. Holcomb, MD, FACS
Vice Chair and Professor of Surgery
Chief, Division of Acute Care Surgery
Director, Center for Translational Injury Research
Jack H. Mayfield, M.D. Chair in Surgery
University of Texas Health Science Center
6410 Fannin, Suite 1100 Houston, TX, 77030
Phone: 713-500-5493
Fax: 713-500-0683
http://www.uth.tmc.edu/cetir/

Houston Data Coordinating Center (HDCC) Principal Investigator:
Barbara C. Tilley, Ph.D.
Lorne C. Bain Distinguished Professor and Director
Division of Biostatistics
University of Texas Health Science Center at Houston
School of Public Health
1200 Herman Pressler Dr., RAS E833
Houston, TX 77030
Phone: 713 500-9564
Fax: 713 500-9530
barabara.c.tilley@uth.tmc.edu

Co-Investigators:
Charles Wade, Ph.D.
Professor of Surgery
University of Texas Health Science Center at Houston

Deborah del Junco, Ph.D.
Associate Professor of Surgery
University of Texas Health Science Center at Houston

Nena Matijevic, Ph.D.
Associate Professor of Surgery
University of Texas Health Science Center at Houston

Erin Fox, Ph.D.
Assistant Professor of Surgery
University of Texas Health Science Center at Houston

Sarah Baraniuk, Ph.D.
Associate Professor for Biostatistics
University of Texas Health Science Center at Houston

Study Locations:

1. Memorial Hermann Hospital/University of Texas Health Science Center – Houston
   PI: Bryan Cotton, M.D., MPH

2. University of California, San Francisco
   PI: Mitch Cohen, M.D.

3. University Hospital Cincinnait
   PI: Pete Muskat, M.D.

4. Sunnybrook Health Sciences Centre/University of Toronto
   PI: Sandro Rizoli, M.D.

5. University of Alabama – Birmingham
   PI: Jeffrey Kerby, M.D.

6. Medical College of Wisconsin
   PI: Karen Brasel, M.D., MPH

7. Oregon Health and Science Unversity
   PI: Martin Schreiber, M.D.

8. University of Tennessee Health Science Center
   PI: Timothy Fabian, M.D.

9. University of Maryland Medical Center
   PI: Thomas Scalea, M.D.

10. University of Arizona
    PI: Terrence O'Keefe, M.D.

11. LA County/ University of Southern California Medical Center
    PI: Kenji Inaba, M.D., FRCSC, FASC

12. Harborview Medical Center
    PI: Eileen Bulger, M.D.

PROTOCOL SYNOPSIS FOR PROPPR: A Resuscitation Outcomes Consortium (ROC) Protocol

Protocol Title	Pragmatic, Randomized, Optimal Platelet and Plasma Ratios
Acronym	PROPPR
Trial Phase	Phase III Trial
Study Sites	At least 12 Level I Trauma Centers in the Phase III Trial
Study Period	Expected start date: March, 2012
Study Population	Trauma subjects predicted to receive massive transfusions (MTs) and enrolled within 2 hours of Emergency Department (ED) admission to Level I Trauma Centers
Objectives	***The objective of this study is to conduct a Phase III multi-site, randomized trial in subjects predicted to have a massive transfusion, comparing the effectiveness and safety of 1:1:1 transfusion ratios of plasma and platelets to red blood cells (the closest approximation to reconstituted whole blood) with the 1:1:2 ratio. The co-primary outcomes will be 24-hour and 30-day mortality. In addition, the functional laboratory and biomarker studies will comprehensively characterize trauma induced coagulation (TIC) and inflammatory milieu providing insight into biological phenotypes, dynamic changes over time and their relationship to treatment and outcome.*** The PROPPR Trial will be conducted under exception from informed consent ([EFIC], Appendix 1) and begin with a Vanguard Stage that will continue for up to six months to assess sites' ability to implement the protocol and recruit subjects. **Clinical Hypotheses and Aims** **Primary Clinical Aim:** To separately compare as co-primary outcomes, 24-hour mortality and 30-day mortality between 1:1:1 and 1:1:2 groups adjusting for clinical site. **Primary Clinical Hypothesis 1**: A greater proportion of subjects who are predicted to have a massive transfusion and randomized to the 1:1:1 ratio group will survive to 24 hours after Emergency Department (ED) admission compared with subjects randomized to the 1:1:2 ratio. **Primary Clinical Hypothesis 2**: A greater proportion of subjects who are predicted to have a massive transfusion and randomized to the 1:1:1 ratio group will survive to 30 days after ED admission compared with subjects randomized to the 1:1:2 ratio. **Ancillary Clinical Aim:** To compare subjects predicted to have a massive transfusion and randomized to the 1:1:1 or 1:1:2 ratio groups on a variety of ancillary clinical outcomes measured from randomization to initial hospital discharge after adjusting for site. **Ancillary Clinical Hypotheses 1:** Subjects predicted to have a massive transfusion and randomized to 1:1:1 will differ in number of hospital-free, ventilator-free, and ICU-free days from the 1:1:2 ratio group. **Ancillary Clinical Hypothesis 2:** Subjects predicted to have a massive transfusion and randomized to the 1:1:1 and 1:1:2 ratio groups will differ in time to hemostasis, major surgical procedures, and in the incidence of transfusion-related serious adverse events during initial hospitalization; will differ in the amount of study blood products given until hemostasis and in the amount of blood products given from hemostasis to 24 hours; and will differ in functional status at initial hospital discharge and in initial hospital discharge status. **Laboratory Hypotheses and Aims** **Overall Laboratory Hypothesis:** Subjects predicted to have a massive transfusion will differ in their coagulation and inflammatory phenotypes at admission and over time which

	will be affected by resuscitation and affect outcome. **Laboratory Aim 1:** To develop models characterizing TIC and inflammation in enrolled patients at ED admission. **Hypothesis 1:** Severely injured trauma patients enrolled into PROPPR will differ in their coagulation and inflammatory phenotypes at admission by subjects' demographic and baseline injury characteristics. **Laboratory Aim 2:** To develop models characterizing the dynamics of TIC in order to identify mechanistic drivers and sequelae of coagulation and inflammation, AND to characterize the natural history of the coagulation/inflammatory milieu in enrolled subjects. **Hypothesis 2:** Coagulation and inflammatory phenotypes identified at admission will display dynamic changes. These phenotype changes will be driven by injury demographics and resuscitation. **Laboratory Aim 3:** To assess the effect of coagulation and inflammatory models on primary and ancillary outcomes. **Hypothesis 3:** Coagulation and inflammatory profiles identified in **Laboratory Aims 1 and 2** will be associated with primary and ancillary clinical outcomes.
Background	Multiple observational studies have reported that blood product component ratios (*i.e.*, plasma:platelets:RBCs) that approach the 1:1:1 ratio, as found in fresh whole blood, are associated with significant decreases in truncal hemorrhagic death and in overall 24-hour and 30-day mortality among injured patients. [1-17] The rationale for the 1:1:1 ratio is that the closer a transfusion regimen approximates whole blood, the faster hemostasis will be achieved with minimum risk of coagulopathy. The current DoD guideline specifies the use of 1:1:1,[18] and this practice is followed in almost all combat casualties. In other observational studies, leading centers have reported good outcomes across a range of different blood product ratios.[2-6, 9, 19] For example, a 1:2 plasma:RBC ratio is used with little guidance regarding platelets.[19, 20] The American Association of Blood Banks (AABB) recently performed a meta-analysis and recommended the use of at least a 1:3 plasma:RBC ratio in Level I trauma centers until randomized trials can provide more definitive evidence.[21, 22] The proposed randomized trial is intended to resolve debate and uncertainty regarding optimum blood product ratios. Trauma induced coagulopathy (TIC) is the global term that describes coagulopathy after injury and the associated sequalae.[23-25] Despite identification and quantification of this coagulopathy, the initiators of the process, underlying mechanisms, interaction of different coagulopathy phenotypes and their specific relationships to treatment and outcomes remain poorly understood and are a priority research area for the management of trauma hemorrhage. Brohi and Cohen have recently described a proposed mechanism for this TIC based on the protein C pathway.[10, 24, 26] However, a definitive causal link has not been established. Several recent publications have documented the lack of understanding in this critical arena.[27, 28] Underlying the continuing controversy in trauma resuscitation research are two main concerns: transfusion-related complications[29] and survival/selection bias.[30, 31] Some studies have shown <u>decreased</u> rates of complications from multiple organ failure (MOF) with increased ratios of blood products,[2, 4, 5] while others have documented <u>increased</u> MOF rates.[9, 19] A few studies recorded data only on patients who survived at least 48 hours, focusing on inflammatory outcomes of acute respiratory distress syndrome (ARDS) and MOF. Other studies excluded only those patients who died in the first 30 minutes after Emergency Department (ED) arrival. Because most preventable hemorrhagic deaths occur

	within hours of trauma patients' ED arrival, it is critical to evaluate both the short- as well as longer-term effects of blood product transfusions. Therefore the longer a bleeding patient survives, the greater the chance to receive a cumulative ratio approaching 1:1:1 (survival bias). **The proposed multi-center, randomized trial with a Vanguard Stage and intent-to-treat (ITT) analyses based on appropriate short- and long-term outcomes will 1) address the survival and selection bias that plagues previous studies, and 2) provide a more complete picture of the effectiveness and safety of 1:1:1 vs. 1:1:2 blood product ratios over the time windows of trauma patients' greatest potential benefit and risk.**
Study Design	Randomized, two-group, controlled Phase III trial with a Vanguard stage. Equal random allocation to treatment using stratified, permuted blocks with randomly chosen block sizes and stratification by site.
Subject Inclusion Criteria	*To be eligible, subjects must meet all of the following:* 1) Required the highest trauma team activation; 2) estimated age 15 years or older or greater than/equal to weight of 50 kg if age unknown; 3) received directly from the injury scene; 4) initiated transfusion of at least one unit of blood component within the first hour of arrival or during prehospital transport; 5) predicted to receive a MT by exceeding the threshold score of *either* the ABC score or the attending trauma physician's judgment criteria.
Subject Exclusion Criteria	*Subjects are ineligible if they meet one or more of the following:* 1) Received care from an outside hospital or healthcare facility (defined as receiving a life saving intervention); 2) Moribund patient with devastating injuries and expected to die within one hour of ED admission; 3) prisoners directly admitted from a correctional facility; 4) Patients requiring an emergency department thoracotomy; 5) Children under the age of 15 years or under 50 kg body weight if age unknown; 6) Known pregnancy; 7) Greater than 20% total body surface area (TBSA) burns 8) suspected inhalation injury; 9) received greater than five consecutive minutes of cardiopulmonary resuscitation (CPR with chest compressions) in the pre-arrival or ED setting; 10) Known DNR prior to randomization; 11) Enrolled in a concurrent ongoing interventional, randomized clinical trial; 12) Have activated the "opt-out" process for the PROPPR trial.
Study Intervention and Duration	A protocol using the 1:1:1 (plasma:platelets:RBCs) compared to the 1:1:2 ratio. Subjects will be followed to hospital discharge or up to the 30th day of hospitalization (whichever comes first) and have a 30-day follow-up mortality assessment.
Primary Outcome Measures	Absolute percent (rather than relative percent) group difference in 24-hour and 30-day mortality (Co-primary outcomes)
Sample Size	Phase III: 580 subjects. 290 subjects/group provide 90% power to detect a difference as small as 10% in 24-hour mortality and 88% power to detect a 12% difference in 30-day mortality, assuming alpha=0.044 (adjusted from 0.05 for 3 interim effectiveness analyses), two sided, and assuming 24-hour and 30-day mortality in the 1:1:1 group of 11% and 23%, respectively based on epidemiologic data. At the DSMB meeting, April 25, 2013, prior to any review of unblinded data the blinded members of the DSMB reviewed a prespecified adaptive analysis conducted by blinded ROC biostatisticians and recommended that the sample size be increased from 580 to 680 to maintain a power of >85%. NHLBI approved this modification.
Analysis	The primary clinical analyses will separately compare treatment group differences in 24-hour and 30-day mortality using Mantel-Haenszel Tests with site stratification. For Laboratory Aims 1-3 we will develop models (reverse-engineered from the laboratory data) to identify drivers and sequelae of TIC and inflammation and to assess relationships among identified phenotypes and outcomes. In addition traditional regression analyses will be conducted for Laboratory Aim 3.

Monitoring Safety	There will be three formal effectiveness analyses. The 2 interim analyses for the DSMB will occur after 1/3 and 2/3 of the projected 24-hour or 30-day mortality events are observed (whichever reaches its projected 1/3 and 2/3 first). The two co-primary outcomes will be separately monitored using a two-sided O'Brien-Fleming boundary with Lan-DeMets alpha spending function based on events for each of the two comparisons.[32] The plan for interim analysis is suggested as a guideline for the DSMB, and could be modified by the DSMB prior to the start of the trial. At each DSMB meeting after the start of the trial, we will present safety data by treatment group (labeled as A,B in the same manner proposed by the 2006 FDA Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committes, unless the DSMB requires complete unblinding). This would include, but is not limited to, total counts of all related, serious and unanticipated adverse events, including a description of the event itself. Additional safety analyses will be developed as requested by the DSMB. We will report overall mortality for the safety analysis. At the formal interim analysis we will report mortality by treatment group (or A,B).

DATA COLLECTION FLOWSHEET

ASSESSMENTS	Pre ED	ED	OR	IR	Inpatient 1st 24 hrs	Inpatient Daily Assess.	Discharge Info	30 Days
Eligibility Criteria	x	x						
Demographics		x					x	
Trauma Activation	x							
EMS Care	x							
Unit arrival information		x	x	x	x			
Informed consent process		x	x	x	x	x		
Vital Signs	x	x	x	x	x	x		
Glasgow Coma Scale	x	x	x	x	x	x	x	
Extended Glasgow Outcome Score							x	
Mortality		x	x	x	x	x	x	x
Life Saving Interventions	x	x	x	x	x	x		
Injury Information	x	x						
Blood Products (including age of product)	x	x	x	x	x	x		
Non-blood Fluids	x	x	x	x	x	x		
Medications	x	x	x	x	x	x		
Surgical Procedures			x		x	x		
Interventional Radiology Procedures				x		x		
Angiogram				x				
Lab Results		x	x	x	x	x		
Hemostasis Obtained		x	x	x	x			
*Research Lab Sample Collection		x	x	x	x	x		
Multi-Organ Failure Assessment						x		
Complications					x	x	x	
Injury Severity Score (ISS)							x	
Subject Disposition							x	
Past Medical History							x	

* Research lab samples time points:
For all subjects (screened, eligible, or randomized): 0 hour
For all randomized subjects: 2, 4, 6, 12, 24, 48, and 72 hours

1. OVERVIEW

The Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR) study design is a Resuscitation Outcomes Consortium (ROC) Protocol. ROC is funded by the National Heart, Lung. and Blood Institute (NHLBI), the United States' Department of Defense (DoD) and the Defence Research and Development Canada. ROC is a clinical trial network focusing on research primarily in the area of pre-hospital cardiopulmonary arrest and severe traumatic injury. Its mission is to provide infrastructure and project support for clinical trials and other outcome-oriented research in the areas of cardiopulmonary arrest and severe traumatic injury that lead to evidence-based change in clinical practice (https://roc.uwctc.org/tiki/tiki-index.php). PROPPR will be conducted as a Phase III trial at Level I Trauma Centers in North America. The Phase III trial is designed to evaluate the difference in 24-hour and 30-day mortality among subjects predicted to receive massive transfusion ([MT] defined as receiving 10 units or more RBCs within the first 24 hours). The goal of PROPPR is to improve the basis on which clinicians make decisions about transfusion protocols for massively bleeding patients.

2. SPECIFIC AIMS AND HYPOTHESES

The objective of this study is to conduct a Phase III multi-site, randomized trial in subjects predicted to have a massive transfusion, comparing the effectiveness and safety of 1:1:1 transfusion ratios of plasma and platelets to red blood cells (the closest approximation to reconstituted whole blood) with the 1:1:2 ratio. The co-primary outcomes will be 24-hour and 30-day mortality. In addition, the functional laboratory and biomarker studies will comprehensively characterize the post-trauma coagulation and inflammatory milieu providing insight into biological phenotypes, dynamic changes over time and their relationship to treatment and outcome. The PROPPR Trial will be conducted under exception from informed consent (EFIC) and begin with a Vanguard Stage that will continue for up to six months to assess sites' ability to implement the protocol and recruit subjects.

Clinical Hypotheses and Aims

Primary Clinical Aim: To separately compare as co-primary outcomes, 24-hour mortality and 30-day mortality between 1:1:1 and 1:1:2 groups adjusting for clinical site.

Primary Clinical Hypothesis 1: A greater proportion of subjects who are predicted to have a massive transfusion and randomized to the 1:1:1 ratio group will survive to 24 hours after Emergency Department (ED) admission compared with subjects randomized to the 1:1:2 ratio.

Primary Clinical Hypothesis 2: A greater proportion of subjects who are predicted to have a massive transfusion and randomized to the 1:1:1 ratio group will survive to 30 days after ED admission compared with subjects randomized to the 1:1:2 ratio.

Ancillary Clinical Aim: To compare subjects predicted to have a massive transfusion and randomized to the 1:1:1 or 1:1:2 ratio groups on a variety of ancillary clinical outcomes measured from randomization to initial hospital discharge after adjusting for site.

Ancillary Clinical Hypotheses 1: Subjects predicted to have a massive transfusion and randomized to 1:1:1 will differ in number of hospital-free, ventilator-free, and ICU-free days from the 1:1:2 ratio group.

Ancillary Clinical Hypothesis 2: Subjects predicted to have a massive transfusion and randomized to the 1:1:1 and 1:1:2 ratio groups will differ in time to hemostasis, major surgical procedures, and in the incidence of transfusion-related serious adverse events during initial hospitalization; will differ in the amount of study blood products given until hemostasis and in the amount of blood products given from hemostasis to 24 hours; and will differ in functional status at initial hospital discharge, and in initial hospital discharge status.

Laboratory Hypotheses and Aims

Overall Laboratory Hypothesis: Subjects predicted to have a massive transfusion will differ in their coagulation and inflammatory phenotypes at admission and over time which will be affected by resuscitation and affect outcome.

Laboratory Aim 1: To develop models characterizing TIC in enrolled patients at ED admission.
Hypothesis 1: Severely injured trauma patients enrolled into PROPPR will differ in their coagulation and inflammatory phenotypes at admission by subjects' demographic and baseline injury characteristics.

Laboratory Aim 2: To develop models characterizing the dynamics of TIC in order to identify mechanistic drivers and sequelae of coagulation and inflammation, AND to characterize the natural history of the coagulation/inflammatory milieu in enrolled subjects.
Hypothesis 2: Coagulation and inflammatory phenotypes identified at admission will display dynamic changes. These phenotype changes will be driven by injury demographics and resuscitation.

Laboratory Aim 3: To assess the effect of coagulation and inflammatory models on primary and ancillary outcomes.
Hypothesis 3: Coagulation and inflammatory profiles identified in **Laboratory Aims 1 and 2** will be associated with primary and ancillary clinical outcomes.

3. BACKGROUND

Injury is the leading cause of death in adults and children between the ages of 1 and 44 years. Nearly 50% of injury-related deaths occur before the individual reaches the hospital, and much of this mortality may remain difficult to prevent.[7, 33-36] However, approximately 40% of the in-hospital deaths among injured patients involve massive truncal hemorrhage that is considered potentially salvageable.[37-43] The staggering numbers of years of productive life lost due to hundreds of thousands of deaths annually from injuries (over 180,000 in the U.S. in 2007) demands more urgent attention to this major public health problem.[44-48] In the late 1970s, whole blood was the primary resuscitation fluid for exsanguinating patients. Due to the concern for potential infectious diseases among donors, component therapy using separated units of RBCs, plasma and platelets, has become the standard in Level I Trauma Centers. However, no randomized trial has ever been conducted to establish which of the many different component transfusion regimens possible is best for trauma patients. Increasing knowledge of the myriad factors influencing survival and recovery following traumatic injury has focused clinical and translational research on the modifiable aspects of resuscitation and transfusion protocols.[49, 50]

Epidemiology of Trauma

In an autopsy study from the ongoing conflicts in Iraq and Afghanistan, fully 86% of all potentially preventable deaths were from truncal hemorrhage.[41] Likewise, in the civilian arena, the leading cause of potentially preventable death is early truncal hemorrhage,[37] with most deaths occurring within 6-12 hours of admission (Figure 1).[6, 37]

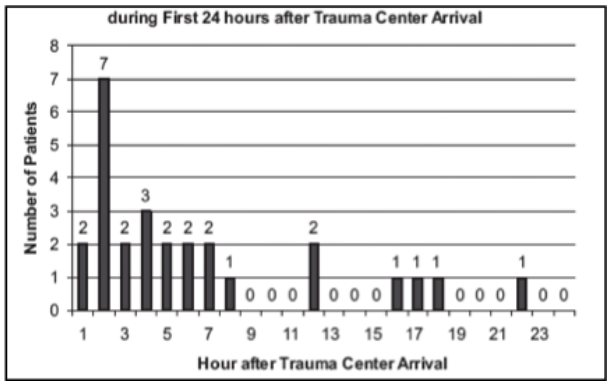


Figure 1. Mortality distribution of Massive Transfusion patients (n=27) during the first 24 hours after trauma center arrival.[6]

A recent paper by Moore et al documents that the majority of massive transfusion (MT) patients traditionally receive ≥ 10 units of blood in the first 6 hours after injury and have the highest incidence of death during the same time frame (Figure 1).[6] Likewise, civilian data from Los Angeles County document that early death is largely from hemorrhage and occurs early after admission, while late death is uncommon.[37] Unpublished data from University of Texas Health Science Center at Houston (UTHealth) has demonstrated that the majority of these deaths occur within the first 24 hours of admission, and very few occur after 72 hours (Figure 2). Data from Perkins and Spinella show a similar timeline in military casualties,[51, 52] while Holcomb

and Kelly have shown that truncal hemorrhage is the leading potentially preventable cause of death in U.S. military casualties.[39, 41]

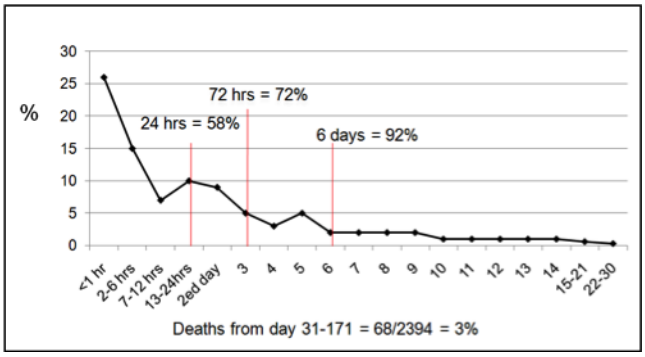


Figure 2. UTHealth-Houston 1999 – 2008 Trauma admissions = 26,028 and 2,394 deaths = 6.6%

Trauma Induced Coagulopathy

Coagulopathy likely plays a significant role in preventable deaths due to hemorrhage, as seriously injured patients in shock are the ones who most often present with coagulopathy in the ED. Trauma patients who are not coagulopathic rarely die. Trauma induced coagulopathy (TIC) is the global term that describes coagulopathy after injury and the associated sequalae.[23-25] Previous studies have defined TIC as increases in plasma based coagulation tests (activated partial thromboplastin time [APTT], partial thrombin time [PTT], prothrombin time [PT] and international normalized ratio [INR]).[53] Identifiable coagulopathic alterations occur nearly immediately after injury and are associated with significant bleeding, morbidity, and mortality. Despite identification and quantification of this coagulopathy, the initiators of the process, underlying mechanisms, interaction of different coagulopathy phenotypes and their specific relationships to treatment and outcomes remain poorly understood and are a priority research area for the management of trauma hemorrhage. Brohi and Cohen have recently described a proposed mechanism for this TIC based on the protein C pathway.[10, 24, 26] However, a definitive causal link has not been established. Several recent publications have documented the lack of understanding in this critical arena.[27, 28] Lack of a mechanistic understanding has likely contributed to the variability in transfusion practice in seriously injured patients, with survival ranging from 40-70%.[5]

Recently, it has been recognized that severely injured trauma patients present with early evidence of a coagulopathy that is heterogeneous based upon age, gender, physiology and mechanism of injury. Two recent studies have identified that TIC is present on arrival in the emergency department in 25% of patients with major trauma.[54, 55] It is associated with *higher* transfusion requirements, a *greater* incidence of multiple organ failure (MOF), *longer* intensive care unit (ICU) and hospital stays, and a 4x risk of mortality compared to those with normal coagulation.[24, 27, 54-56] While it is clear the coagulopathy after trauma is multifactorial and there are several acute coagulopathic phenotypes (each with different diagnoses and treatment modalities), little attention has been directed towards understanding the mechanisms involved with the early presentation of TIC. Thus, laboratory studies of coagulopathy will help define the understanding of the mechanisms of early coagulopathy associated with trauma, how best to mitigate and reverse the effects, and start describing optimal treatment regimens. Furthermore, at the TransAgency Coagulopathy meeting (April 5-6, 2010, http://www.nhlbi.nih.gov/meetings/workshops/tactrauma.htm), the NHLBI and DoD devoted significant time and discussion to this subject and the recommendations drawn from that two day seminar closely parallel the proposed, extensive laboratory effort described later (5.2.6 Laboratory Evaluations).

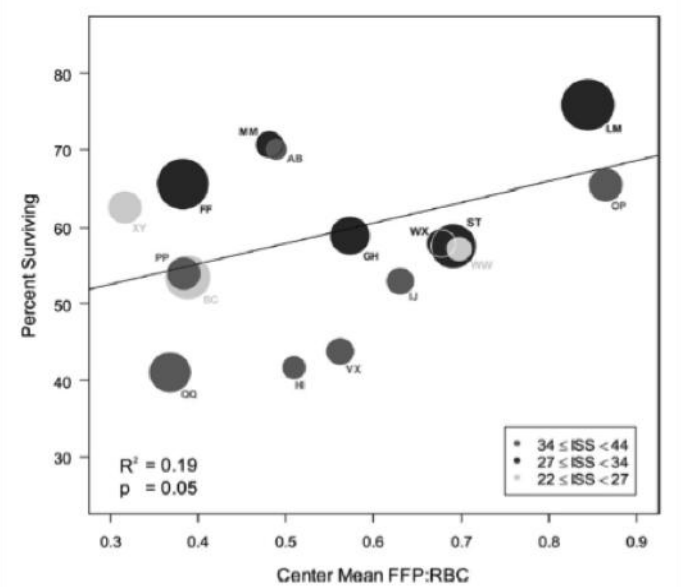


Figure 3. Bubble plot of the relationship of mean center plasma to RBC ratio to survival. Circle size represents the percentage of MT patients contributed by each center. Shades of gray indicate 3 levels of injury severity scores.[5]

Current Transfusion Practices and Ratios

Despite great advances in resuscitation practices over the course of the last half-century, recent data suggest that aggressive use of crystalloid and late and/or inadequate use of plasma and platelets may contribute to increased coagulopathic bleeding and death. A recent study of combat-injured

casualties from Iraq who received MTs revealed that those who received more plasma demonstrated much lower mortality (19%) than those who received more traditional ratios of plasma (65%).[1] Perkins, Borgman, and colleagues reported that increased platelet ratios were associated with improved survival after combat injury.[1, 7] Schnuriger and Holcomb have shown similar data in civilian trauma patients, associating improved survival with increased use of platelets.[5, 8] Holcomb et al recently conducted a multicenter retrospective study of modern transfusion practice at 16 leading civilian trauma centers.[5] Data were collected for all trauma patients admitted in the years 2005-2006 who arrived at the hospital directly from the scene and received at least 1 unit of blood product within 24 hours of admission.[5] From that 12 month period, 466 MT patients were analyzed and it was found that plasma:platelet:RBC ratios varied from 1:1:1 to 0.3:0.1:1, with corresponding survival rates ranging from 71% down to 41%.[5] Importantly, at the center level, mortality was significantly correlated with mean blood product ratios (Figure 3).[5]

Increased plasma and platelet to RBC ratios significantly decreased truncal hemorrhagic death and 30-day mortality without a concomitant increase in MOF as cause of death (Table 1)[5] These data document the relationship between increased survival and increased use of plasma and platelets; however these data may suffer from potential survival bias.[5] Similar to the Borgman military study,[1] patients receiving increased plasma and platelets showed improved 24-hour and 30-day survival, decreased incidence of hemorrhagic death, without an increase in MOF death. Intensive Care Unit free days also were increased in the patients receiving higher plasma and platelet ratios.

	High Plasma (%)		Low Plasma (%)		
	High Platelets n = 151	Low Platelets n = 101	High Platelets n = 83	Low Platelets n = 131	p-Value
Plasma:Platelet:RBC ratio	1:1:1	1:0.2:1	0.3:1:1	0.3:0.1:1	
Survival (%)	71	52	66	41	<0.001
Survival at 6 hours	98	86	83	58	<0.001
Survival at 24 hours	87	75	77	50	<0.001
Survival at 30 days	73	54	68	43	<0.001
Median Time to death, (hours)	35	18	6	4	<0.001
Mortality Rates (%) by Cause of Death					
Truncal Hemorrhage	**10**	25	22	44	<0.001
Head Injury	13	15	**6**	14	0.3
MOF	5	7	6	3	0.45
Airway	0	1	2	2	0.24
Other	3	6	4	4	0.85
Clinical Outcomes					
Hospital free days	6 ± 8	3 ± 6	5 ± 8	3 ± 7	<0.001
ICU free days	5 ± 7	3 ± 6	6 ± 7	4 ± 7	<0.001
Ventilator free days	6 ± 8	2 ± 5	7 ± 8	4 ± 7	<0.001

Table 1. Survival, cause of death, and clinical outcomes by plasma and platelet ratio. High plasma or platelet to RBC ratio ≥ 1:2. Low plasma or platelet to RBC ratio < 1:2.[5]

Multiple observational studies have reported that blood product component ratios (*i.e.*, plasma:platelets:RBCs) that approach the 1:1:1 ratio, found in fresh whole blood, are associated with significant decreases in truncal hemorrhagic death and in overall 24-hour and 30-day mortality among injured patients.[1-17] The rationale for the 1:1:1 ratio is that the closer a transfusion regimen approximates whole blood, the faster hemostasis will be achieved with minimum risk of coagulopathy. The current DoD guideline specifies the use of 1:1:1,[18] and this practice is followed on almost all combat casualties. In other observational studies, leading centers have reported good outcomes across a range of different blood product ratios.[2-6, 9, 19] Additionally, little guidance regarding platelets is available.[19, 20] The American Association of Blood Banks (AABB) recently performed a meta-analysis and recommends the use of at least 1:3 plasma:RBC ratios in Level I trauma centers until randomized trials can provide more definitive evidence.[21, 22] The continuing debate and uncertainty regarding optimum blood product ratios reflect equipoise and support for our proposed randomized trial of the relative effectiveness of the 1:1:1 and 1:1:2 blood product ratios.

Underlying this unresolved controversy in trauma resuscitation research are two main concerns: transfusion-related complications[29] and survival/selection bias.[30, 31] Some studies have shown decreased rates of complications from multiple organ failure (MOF) with increased ratios of blood products,[2, 4, 5] while others have documented increased MOF rates.[9, 19] A few studies recorded data only on patients who survived at least 48 hours, focusing on inflammatory outcomes of acute respiratory distress syndrome (ARDS) and MOF. Other studies excluded only those patients who died in the first 30 minutes after Emergency Department (ED) arrival. Because most preventable hemorrhagic deaths occur within hours of trauma patients' ED arrival, it is critical to evaluate both the short- as well as longer-term effects of blood product transfusions. The longer a bleeding patient survives, the greater the chance to receive a cumulative ratio approaching 1:1:1 (survival bias).

The preponderance of the recent literature suggests patients in severe HS may benefit from increased ratios of plasma and platelets to RBCs. Other reviews and single center reports from leading institutions provide an alternative view, suggesting that a 1:3 ratio be used.[19, 20] Some of these studies have small numbers of MT patients, collected over many years, or exclude all deaths prior to ICU arrival.[57, 58] Conflicting findings in this area are expected since all the studies are retrospective and confounded by multiple unmeasured variables. Watson and colleagues from the Glue grant consortium reported increased MOF rates with increased transfusion of plasma, when excluding patients who died in the first 24 hours.[59] However, increased plasma use was associated with improved survival when the first 24 hours was included in the analysis. Since the majority of bleeding and early death occurs within the first 24 hours, most authors have included this time frame in their analysis. It is also understood that damage control resuscitation (DCR) should not be performed in patients who are not in HS or are not at high risk of massive bleeding, as the increased plasma and platelets could increase MOF, without a survival benefit.

Defining a Massive Transfusion Study Population

The need for MT can be rapidly predicted, using data available within minutes of arrival in the ED in both blunt and penetrating military and civilian casualties (Table 2).[49, 60-64] In combat casualties with penetrating injuries Schreiber, Wade, and McLaughlin have all documented a receiver operator characteristic area under the curve (AUC) of 0.8 using easily available variables, systolic blood pressure (SBP) < 110, heart rate (HR) > 105, hematocrit (Hct) < 32, pH < 7.25.[49, 62, 63] Yücel and Moore showed similar results in a civilian, largely blunt injured population.[6, 64] Nunez and colleagues have created the most rapidly acquired score, the assessment of blood consumption score (ABC score), not requiring any laboratory values and with a high value on the receiver operator characteristic curve.[61]

Table 2. Summary of Reported Receiver Operating Characteristic AUC Values in Trauma

Author	Variables	AUC*
McLaughlin et al.[49]	SBP, HR, pH, Hct	0.77
Yücel et al.[64]	SBP, HR, Base Deficient (BD), Hemoglobin (Hgb), Male, +FAST (Focused Assessment for the Sonography of Trauma), long bone/pelvic fracture	0.84
Moore et al.[6]	SBP, pH, ISS>25	0.80
Schreiber et al.[62]	Hgb≤11, INR>1.5, penetrating injury	0.80
Wade et al[63]	SBP, HR, pH, Hct	0.78
Nunez et al[61]	SBP, HR, FAST, penetrating mechanism	0.85
Nunez et al[60]	SBP, HR, FAST, penetrating mechanism, RBC transfusion in ED	0.89

*AUC is a function of specificity and sensitivity.

Clinically, the ability to accurately predict which patients will or will not require MT is important so that increased plasma and platelet transfusions can be started early in those who will potentially benefit and avoided in those who will not.[6, 49, 62-64] In a randomized study, this algorithm is necessary for accurate randomization and decreasing noise from minimally transfused patients. Recognizing this important issue, efforts to develop ever more accurate MT prediction algorithms are ongoing at several leading centers.

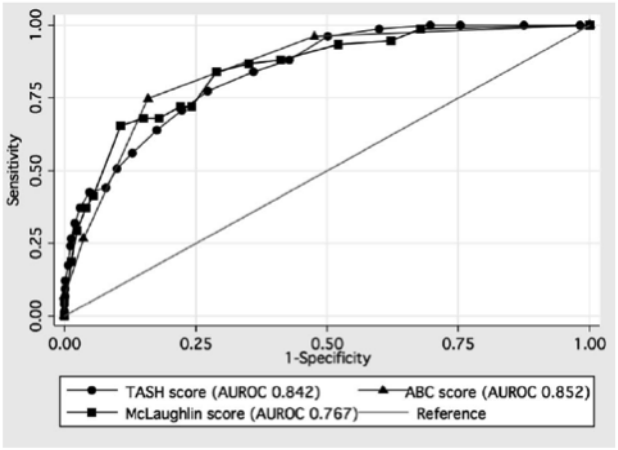


Figure 4. AUC for three different scoring systems[58]

Nunez et al have recently published the simplest MT prediction model using only data routinely available within 5-10 minutes of patient arrival in any trauma center and not relying on the use of any laboratory values.[61] This same group also describes the additional benefit of using a unit of RBC transfused in the ED and the ABC score to improve the prediction of MT patients,

raising the AUC to 0.89.[60] The ABC score is comparable to other algorithms with more complicated and time-consuming data requirements (Figure 4); however it holds the added benefit of not being delayed by laboratory testing that could delay the correct treatment. This scoring system has also been recently been validated in a multicenter, retrospective study.[65] **PROPPR will utilize ED RBC transfusion combined with the validated ABC score or physician assessment to randomize patients**.

Risks and Complications of Transfusion

Few interventions in medicine are without risk. The risk of transfusion-related acute lung injury (TRALI) is increased as plasma and platelets use increases. Most authors estimate a risk of TRALI in 1:10,000 units of FFP transfused, which must be placed in the context of significantly improved survival reported in many recent trauma publications.[25,66] A likely contributor to the improved outcome seen with increased plasma and platelet use is the decrease in excessive crystalloid infusion.[67] Currently, in seriously injured patients the potential benefit of increased blood product transfusion seems to outweigh the known risks.

Rationale for PROPPR Trial

In summary, it is unclear what the optimal ratio should be, and several leading centers have described good outcomes with both higher and lower ratios, confirming the presence of clinical equipoise for the proposed study groups.[2-6, 9, 19, 49] It is critical to understand that Level I/II data from clinical trials are completely lacking in this area, and this proposal addresses the issue.

Clinical Rationale

Currently, there is no universally accepted MT guideline. Most trauma centers are using a ratio driven massive transfusion protocol for the early management of bleeding trauma patients rather than a laboratory-directed approach. This is based on the unavoidable delay in obtaining relevant clinical laboratory values.[68] This delay, which can extend up to 45 minutes, prevents reliable goal directed therapy. At least one center (Sunnybrook Health Science Center, Toronto, Canada [NCT00945542]) is studying goal directed therapy, to evaluate clinical efficacy. Based on our experience with a systematic research program starting with an international symposium focused on MT in 2006,[69] followed by a multicenter retrospective study[5] and in 2009, a prospective, observational study (*i.e.*, Prospective, Randomized, Observational, Multicenter, Massive Transfusion sTudy [PROMMTT], Rahbar, Principal Investigator,), substantial variation in mortality rates, blood product ratios and clinical practice persists across many Level I Trauma centers in the U.S., despite the call for a common massive bleeding protocol.[28, 70] [Results from the PROMMTT study provided in this protocol are in draft stage only and have not yet undergone the signed endorsement of all co-investigators, peer-review or publication in a scientific journal.] The proposed study seeks to extend the success of the ROC and draw on important lessons learned (execution of multicenter studies, the use of public notification and community consultation, transfusion study intricacies, web-based data entry and their efficient organization) to conduct the first multi-center, randomized clinical trial (RCT) of varying blood product ratios for the treatment of massively bleeding trauma patients, starting in the ED. Unpublished data from PROMMTT reveal that the proposed ratios in this proposal are representative of current clinical practice at leading trauma centers. **Our proposed Phase III RCT is designed to 1) provide a valid and efficient clinical trial design framework for in-hospital trauma research (including a Vanguard [feasibility] stage), 2) address the survival/selection bias present in previous studies, 3) reduce the risk of post-transfusion complications and conserve resources by restricting enrollment to patients who screen positive on our predictive MT algorithm, 4) contribute to an evidence-based guideline for the treatment of massively bleeding trauma patients, and 5) elucidate the mechanisms of TIC and inflammation.**

The ED setting is a unique environment that introduces challenges to trial design and sample collection, including the use of exception from informed consent (EFIC). The ROC investigative team has extensive experience with both waiver of consent and emergency resuscitation trials. This is the first multicenter RCT of varying blood product ratios of massively bleeding patients using EFIC in the ED. The Vanguard approach is being used for the first time in a trauma trial to improve trial efficiency and increase the likelihood that the trial will be completed and informative.

Additionally, this trial includes the first use of ED RBC combined with the *validated* ABC score[61] or clinical judgment in a prospective, randomized study to predict patients who will or will not require MT. This study will use the full potential of the ABC Score, as it is able to be obtained quickly and without delays from laboratory testing. Based on PROMMTT data, the combination of either a positive ABC score or a trauma physician's gestalt at the time of admission should provide sensitivity=85%, specificity=39%, positive predictive value (PPV) = 30%, and negative predictive value 89% for predicting a trauma patient's need for MT. An 85% sensitivity is higher than any other studies. While the PPV (and 62% AUC) based on PROMMTT data is lower than other studies, the PPV (and AUC) in PROPPR is expected to be considerably higher than 30% because potentially eligible patients who die or achieve hemostasis before the seal on the PROPPR container (containing randomized blood products from the blood bank) is broken will be excluded. The PROPPR protocol enables an unbiased exclusion of many patients who do not require an MT (false positives) and facilitates the appropriate focus on the most seriously hemorrhaging trauma patients at highest risk of mortality and with the greatest potential benefit from optimized blood product ratios. Identification of patients in need of MT is important so that increased plasma and platelet transfusions can be started early in those who will potentially benefit and avoided in those who will not.[6, 49, 62-64] In a randomized study, this algorithm is intended to ensure accurate selection of the massively bleeding patient and increase the signal-to-noise ratio.

Research Laboratory Rationale

Successful resuscitation of massively bleeding trauma patients is constrained also by the gap in our knowledge of the complex interplay between trauma-induced coagulopathy (TIC), inflammation and blood product transfusions. Presently there is incomplete characterization of the multiple coagulopathic phenotypes, understanding of the mechanism for development of coagulopathy, and minimal prospective data to understand or target the putative benefits of early plasma based resuscitation on injured patients. Preventing TIC (e.g., with earlier plasma and platelet transfusions and less crystalloid infusions) is especially challenging when the most sensitive biomarkers of coagulation and inflammation await discovery.[27, 70] This point is clinically important because it is impossible to optimize therapeutic effectiveness to control bleeding, impossible to understand biologically and physiologically the results of our clinical trial and impossible to minimize the risks of late thrombotic, infectious, and inflammatory complications without completely understanding the spectrum of coagulation abnormalities seen after severe injury and the effects of plasma resuscitation on mitigating those perturbations. Identification of the precise targets for the most effective therapies (e.g., an optimum combination of infusions and transfusions), will require vigilant tracking of the time-dependent perturbations in coagulation and inflammation as varying ratios are transfused, hemostasis is achieved and normal hemodynamics restored. With respect to coagulopathy, it is clear that TIC is multifactorial and there are likely several acute coagulopathic phenotypes (each with different diagnoses and treatment modalities), but little systematic attention has been directed towards understanding the mechanisms involved with the early presentation of TIC. Thus, laboratory studies of coagulopathy will help define the understanding of the mechanisms of early coagulopathy associated with trauma, how best to mitigate and reverse the effects, and start describing optimal treatment regimens. This study **will be the first** to characterize the natural history of coagulopathy and inflammation and simultaneously identifies key and novel pathways and therapeutic targets. We will collect blood from severely injured patients immediately after injury and sequentially for 72 hours, a novel venture that will provide data never before collected. Plasma will be assayed for coagulation factors and inhibitors, complement proteins and inflammatory mediators. Measures of coagulation, blood cellular populations and platelet function will be done on fresh whole blood. More specifically, we have chosen to study groups of markers in four main areas: *1) markers of endothelial dysfunction, 2) cytokines and chemokines, 3) parameters of coagulation, including platelet function and 4) mobilization of progenitor cell populations and characterization of circulating cellular populations.* Analyzing these laboratory measures will answer the following questions: 1) How does plasma ratio and resuscitation regime affect TIC and clinical outcome? 2) How does resuscitation (plasma ratio) affect markers of endothelial injury, inflammation and coagulation? 3) How does resuscitation affect cell mobilization and function? 4) How do markers of vascular and circulating cell injury, coagulation, and inflammation change in severely injured patients? Additionally, clinical data that is collected will be utilized to develop a systems level natural history characterization of coagulopathy after injury and identify key and novel pathways and therapeutic targets. By comparing functional coagulation and plasma protein measurements with physiologic measures as well as outcome data we will obtain for the first time a complete picture

of the timing, severity and causes for early coagulopathy, later inflammation, infection and organ failure (Ancillary Clinical Outcomes) after severe trauma and shock.

4. RESEARCH DESIGN

PROPPR is a two-group, 580 patient, randomized, controlled Phase III trial. The rationale for the 1:1:1 ratio is that the closer a transfusion regimen approximates whole blood, the faster hemostasis will be achieved with minimum risk of coagulopathy. The current DoD guideline specifies the use of 1:1:1,[18] and this practice is followed on almost all combat casualties. In other observational studies, leading centers have reported good outcomes across a range of different blood product ratios.[2-6, 9, 19] For example, a 1:2 plasma:RBC ratio is used (albeit with little guidance regarding platelets).[19, 20]

The continuing debate and uncertainty regarding optimum blood product ratios reflect equipoise and support for our proposed randomized trial of the relative effectiveness and safety of the 1:1:1 and 1:1:2 blood product ratios. The distribution of plasma:RBC ratios among PROMMTT patients was heavily clustered around the most commonly occurring ratios of 1:1 and 1:2 (Figure 5A). The distribution of platelet:RBC ratios was more variable with less clustering around 1:1 and 1:2. The PIs of the Level I trauma centers selected for PROPPR unanimously declared equipoise and a preference for comparing 1:1:1 with 1:1:2 plasma:platelet:RBC ratios over any others (Figure 5B).

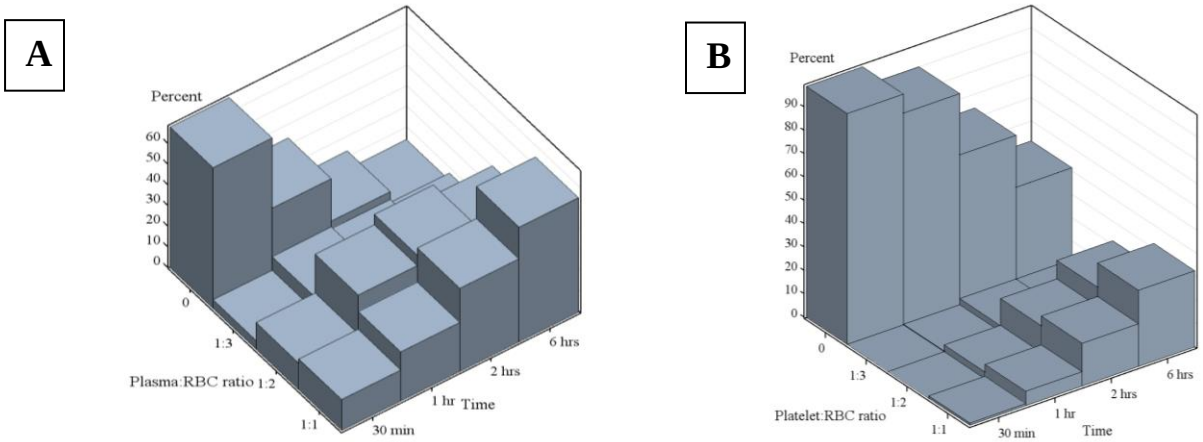


Figure 5. Distribution of plasma (A) and platelet (B) ratios given to substantially bleeding PROMMTT patients by time since admission (ratios in patients who died before the reference time are excluded from the distribution). This three-dimensional figure illustrates the time-varying nature of plasma transfusions conditional on survival. At 30 minutes after ED admission, nearly 70% of patients who have received at least 1 unit of RBCs have not yet received any plasma. In contrast, by 6 hours over 90% have received at least one unit of plasma and over 50% have achieved a 1:1 ratio of plasma to RBCs. A 1:1 ratio is defined here as greater than a 0.667 ratio of plasma to RBCs and a 1:3 ratio is defined as greater than 0 and less than or equal to 0.333.

4.1 Study Population

The target population is trauma subjects who are admitted to one of the participating sites and who meet the inclusion and exclusion criteria detailed below.

4.2 Setting

Level I trauma centers throughout North America, with previous involvement in trauma studies will participate in the trial. Each site is qualified and ready to proceed with the trial. At the site initiation visit, verification that standard operating procedures are in place and are consistent with the GLUE Grant guidelines before enrollment will begin at that site.

4.3 Inclusion Criteria

To be eligible, subjects must meet ALL of the following

1) Subjects who require the highest trauma team activation at each participating center,
2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown,
3) Received directly from the injury scene,

4) Initiated transfusion of at least one unit of blood component within the first hour of arrival or during prehospital transport, and
5) Predicted to receive a MT by exceeding the threshold score of ***either*** the ABC score or the attending trauma physician's judgment criteria (Table 3).

Table 3. ABC Scoring System. 2 or more points=positive prediction for MT[61]	
heart rate > 120 bpm	1 point
systolic blood pressure ≤ 90 mmHg	1 point
penetrating injury	1 point
positive FAST (intra-abdominal fluid by ultrasonography) exam	1 point

4.4 Exclusion Criteria

Subjects are ineligible if they meet one or more of the following

1) Received care (as defined as receiving a life saving intervention) from an outside hospital or healthcare facility (Procedures and care given at an outside health facility cannot be documented or controlled resulting in a high variability of standards of care and clinical outcomes.)
2) Moribund patient with devastating injuries and expected to die within one hour of ED admission; for example, those subjects with lethal traumatic brain injury deemed futile care by the neurosurgery or trauma attending prior to CT scanning or intracranial pressure monitoring, e.g. near decapitation, massive loss of intracranial contents, or transcranial gunshot wounds. Clinical assessment of severity of injury and not pupil reactivity has been found relevant in predictive models.[71, 72] Elderly subjects with massive myocardial infarction or stroke and severe injury based on the assessment of the trauma attending prior to randomization will also be excluded from randomization. (Those with non-survivable injuries or declared dead within 60 minutes of admission are unlikely to receive a MT.)
3) Prisoners, defined as those who have been directly admitted from a correctional facility (Prisoners are excluded because of their vulnerable population status. A free-living individual who is under police observation as a suspect will remain in the study until discharge or incarcerated.)
4) Patients requiring an emergency department thoracotomy (Trauma patients requiring an emergency department thoracotomy have exsanguinated from large vessel injury, have an extremely high mortality and usually do not survive, irrespective of treatment.)
5) Children under the age of 15 years or under 50 kg body weight if age unknown (Subjects under 15 years of age will be excluded, as the majority of adult trauma centers consider age 15 or older to be an adult and would not admit those under age 15. However, this will allow the inclusion of subjects 15 to 17 year olds that are at a high risk of motor vehicle accidents causing blunt or penetrating injuries and are admitted to Trauma Centers.)
6) Known pregnancy in the ED (Pregnant women have a significantly increased intravascular volume and physiologic reserve for bleeding which can require adjustments to the standard treatment protocols. Therefore for consistency for data analysis, pregnant women will be excluded.)
7) Greater than 20% total body surface area (TBSA) burns (Subjects with large and severe thermal injuries will require early and aggressive resuscitation to replace intra-vascular volume losses. As such, subjects with both large TBSA burns and traumatic injuries will require a resuscitation approach that is different to current isolated trauma resuscitation strategies. Additionally, in the absence of concomitant severe blunt trauma, these subjects are unlikely to receive blood products in the early resuscitative phase.)
8) Suspected inhalation injury
9) Received greater than five consecutive minutes of cardiopulmonary resuscitation (CPR with chest compressions) in the pre-arrival or ED setting (Subjects who receive greater than five consecutive minutes of CPR in the pre-hospital or initial ED setting are more likely to have non-survivable injuries and are not likely to receive a massive transfusion. Conversely, brief episodes of CPR are not unusual in severely hypotensive subjects.)
10) Known Do Not Resuscitate (DNR) prior to randomization

11) Enrolled in a concurrent, ongoing interventional, randomized clinical trial
12) Patients who have activated the "opt-out" process or patients/legally authorized representatives that refuse blood products on arrival to ED.

5. INTERVENTION (Figure 6)

5.1 Screening Procedures

Clinical research staff will be available in the hospital at each center on a 24/7 basis to conduct screening for PROPPR. The research staff will screen all major trauma subjects admitted to the ED with the highest acuity status. Data collection, blood draw for time 0, and subject observation will begin on the highest acuity subjects immediately upon the patient's arrival to the ED. Once it is determined that the subject is ineligible, data collection will cease. For subjects meeting the PROPPR eligibility criteria, the research staff will perform an assessment using the validated ABC score (Table 3).[61] Subjects with two or more positive variables from the ABC score on admission will be eligible to be randomized in the trial and receive the PROPPR transfusion protocol. The clinical person responsible for implementing physician orders will notify the blood bank per standard procedure at each institution. In subjects with fewer than two of these variables, the PROPPR research staff will query the trauma attending as to their clinical judgment regarding whether the patient will require a MT. If the attending responds with a "yes" the patient will be eligible for the trial. The physician can wait to respond to the gestalt question, if unsure; however, he or she must respond within one hour of ED admission to activate the protocol. If the answer, however, is "no" the patient will be considered ineligible and all study procedures will end. The data collected up to the time the patient is deemed ineligible will be kept at each site and submitted to the HDCC to allow a description of screened patients versus enrolled subjects and provide demographic data for the blood samples analyses. The clinical data required to calculate the ABC score is routinely acquired at Level I trauma centers and should be available within minutes of arrival on all potential subjects.

5.2 Study Procedures

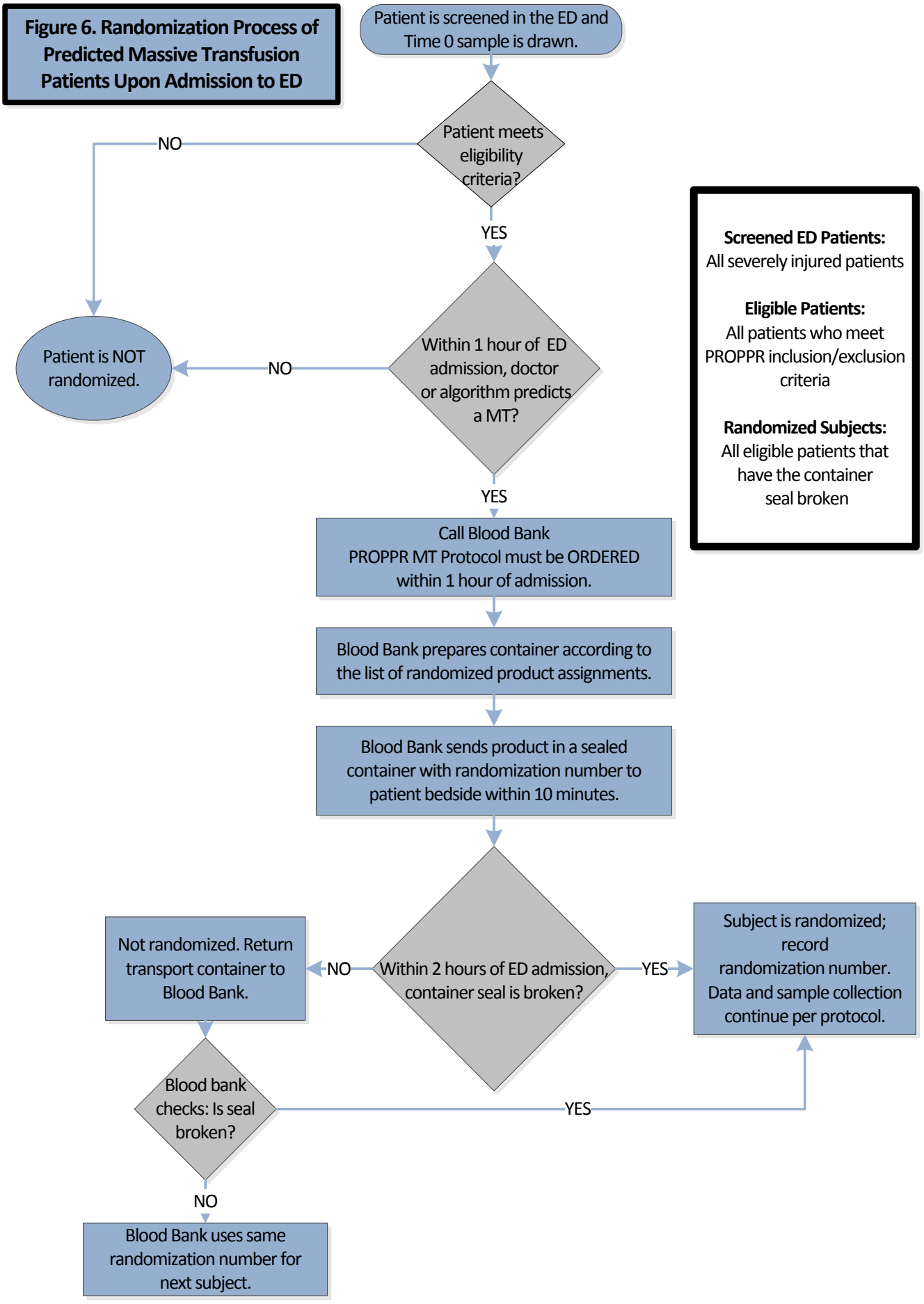
5.2.1 Randomization

A stratified, permuted blocked randomization scheme will be used to assure balance over time in the intervention groups. Block sizes will be randomly chosen to avoid revealing a treatment assignment in this unblinded trial. Randomization will be stratified by site. For consistency in all sites, randomization of blood products will be completed in the blood bank. Randomization lists will be prepared by the UTHealth Data Coordinating Center (HDCC) and sent to the contact person at the blood bank at each site who will keep the codes.

The randomization process for eligible subjects will begin when the attending trauma physician or the ABC score predicts that the patient will receive a MT (Figure 6). In eligible patients with severe injury and profound hypotension, especially with penetrating wounds, scoring systems are not required to predict the need for MT. The attending trauma physician will automatically call for a MT. The clinical staff member will then notify the blood bank to randomize the patient. The person at the blood bank who holds the randomization list will prepare the container using the next subject randomization number on the list and associated blood product assignment, seal the container, and have the container quickly delivered to where the patient is. Platelets may be harmed when placed on ice, therefore, the appropriate amount of platelets will be placed into an opaque container, attached to the transport container. The opening for this container will be sealed as well. The container will be labeled with the subject's randomization number.

If in the opinion of the attending trauma physician, the patient has improved sufficiently to no longer require a massive transfusion, or if the patient had died and thus no longer meets eligibility criteria (and before the container seal is broken), the container will be quickly returned to the blood bank. If the seal is unbroken, the blood products will be returned to their appropriate storage location, the subject's randomization number will be returned to the randomization list, and the next eligible subject will receive the same blood product assignment. Thus, a patient is not randomized into the trial until the container seal is broken.

Figure 6. Randomization Process of Predicted Massive Transfusion Patients Upon Admission to ED



This approach takes into account the rapidly changing physiology of these patients within the first minutes of hospital arrival, minimizes the number of ineligible subjects who will be randomized, followed and included in the intent-to-treat analysis and followed, and minimizes wastage of precious blood products. To help the enrollment and randomization process function smoothly, total quality improvement methodology, such as used in the NINDS t-PA Stroke Trial to reduce time from stroke onset to treatment, will be used in this trial to decrease time from door to randomization and receipt of study blood products.[73] In order to ensure the randomization process is conducted in a consistent manner at all sites, one to two blood bank technicians will be funded to assist the blood bank and enable them to meet the requirements of the clinical research team.

Once the seal on the container is broken, the subject is randomized into the assigned treatment group. The subject will continue to receive products as assigned until: (**1**) the PROPPR transfusion protocol has been discontinued by the trauma attending because hemostasis) has been achieved, (**2**) the subject has died, or (**3**) the patient or LAR refuses continuation in the trial. While the PROPPR transfusion protocol ratio groups are ongoing, no additional plasma, platelets, or RBC will be allowed. When situation 1 is met, additional individual units of plasma, platelets, or RBCs can be transfused, based on institutional guidelines, local laboratory results, and clinical judgment. All resuscitation fluids and blood products transfused pre-hospital and within 24 hours of admission will be recorded.

In the event two or more subjects enter in the ED in close proximity and are both predicted to be a MT patient, the first patient will be randomized and followed. Notation will be made on the screening log regarding why the additional predicted MT patient was missed. In cases where products for all treatment groups are unavailable for transfusion, the blood bank will indicate the patient will not be randomized into the trial.

5.2.2 Blinding

Although it will be impossible to mask intervention assignment at the bedside in a double- or single-blinded manner, concealing the blood products in a sealed container until the moment of actual transfusion will maintain rigor and prevent bias as much as possible, while maintaining the ability to care for these critically ill subjects. To promote blinding, a "sham" platelet bag will be attached to each container that does not contain platelets. Adherence to the treatment protocol will be carefully monitored and protocol deviations will be identified through the data collected or reported to the Houston Data Coordinating Center (HDCC) by study coordinators. The co-primary outcomes, 24-hour and 30-day mortality, are endpoints making blinding less of a concern in terms of outcome assessment.

5.2.3 Initial Blood Release

Usual, approved procedures for the release of blood products will be followed according to each individual site. Rapid utilization of plasma is made possible by keeping 2-4 units of thawed AB plasma available in the ED at all times, and many trauma centers have implemented this practice. Thawed plasma may be stored in a refrigerator for up to 5 days, and in busy hospitals is rarely wasted. A recent report from leading blood banks describe decreasing plasma waste by 80% after implementing a thawed plasma program.[74]

5.2.4 PROPPR Transfusion Protocol (Figures 6&7)

a. Upon notification of a PROPPR subject for randomization, the blood bank will prepare the appropriate treatment group products in a container available for delivery to the subject's bedside. The goal for delivery of the first container is 10 minutes after notification. Total quality improvement methodology will be used to attain this goal.[73] This rapid response requires thawed plasma in the blood bank. If six plasma and platelet and RBC units are not immediately available (based on blood type of patient or availability), the blood bank will issue units that are ready and notify appropriate personnel when the remainder of the units that constitute the first container are available. In the event that ABO/type-specific products are unavailable, universal donor products will be used, in accordance with each blood bank's policy. Based on the requirement for a rapid response, the first container will likely contain uncrossmatched products, including thawed plasma.
b. After the first container leaves the blood bank, the team will then prepare a second container of the same ratio group. This process will automatically be repeated each time the set of components is issued until the

attending trauma physician notifies the blood bank that the PROPPR transfusion protocol is no longer needed. This process will ensure that there is no delay in availability of blood products.

c. The blood containers should follow the subject at all times to prevent duplicate blood orders and unavailability of blood products when needed by the subject. Any subsequent container that was delivered to the subject, but was not needed, will be returned to the blood bank.
d. All standard blood bank laboratory documentation will be completed for all blood products.
e. It is recognized that randomization and organizing the transfusion container will be additional work for the blood bank personnel. Funds have been set aside for additional blood bank technicians to facilitate this process.

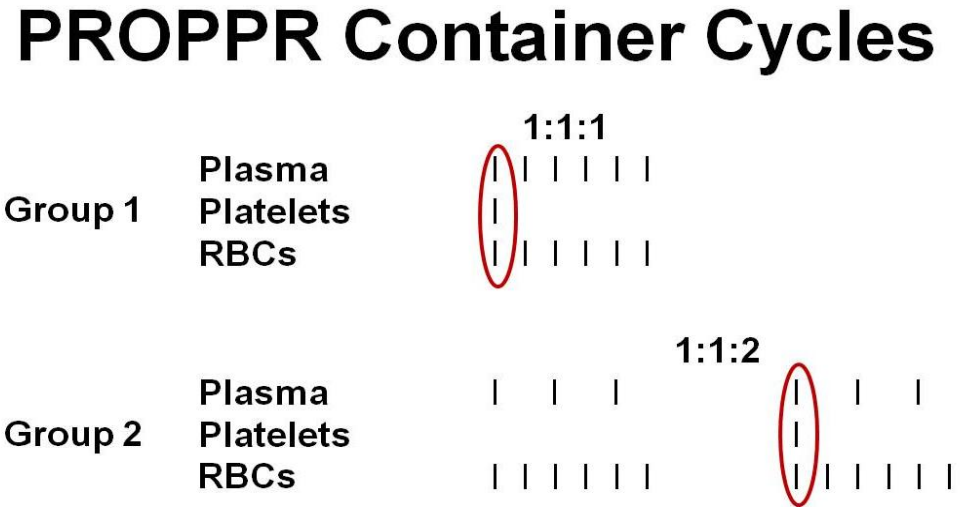


Figure 7 represents one container cycle for each ratio group. Each hash mark represents one unit of blood products. Every 6 units of RBCs represent one container. The red circles indicate when platelets are given. 1 unit of platelets is the equivalent of a pool of 6 units on average. The container cycles repeat until hemostasis is achieved

Products can be serially transfused (platelets, RBC then plasma) or products can be transfused simultaneously.
Group 1 will be randomized to receive the 1:1:1 ratio of plasma:platelets:RBC. For Group 1, the blood bank at each site will prepare the initial container containing 6 units plasma, 1 unit platelets (a pool of 6 units on average) and 6 units RBC; the blood bank will send the initial and all subsequent containers until notified of the discontinuation of the PROPPR transfusion protocol. A laminated card stating, "Transfuse Platelets First" will be attached to the unit of platelets in each container, and subjects are expected to receive one unit of blood product products before the first container arrives (from RBC and plasma available immediately upon ED arrival).

Group 2 will be randomized to receive the 1:1:2 ratio. For Group 2, the blood bank will prepare the initial container containing 3 units plasma, 0 units platelets and 6 units RBC, a second container containing 3 units plasma, 1 unit platelets (a pool of 6 units on average) and 6 units RBC, and the blood bank will send this sequence of 2 containers repeatedly, until notified of the discontinuation of the PROPPR transfusion protocol (Table 4). The laminated card stating, "Transfuse Platelets First" will be attached to the unit of platelets in every 2nd container of the sequence, and subjects are expected to receive the 1st unit of platelets with the 7th unit RBC.

Table 4. PROPPR Trauma Massive bleeding Protocol (Plasma:Platelets:RBC)*

Plasma	As soon as the subject is randomized for a massive transfusion Group 1 = For every 6 plasma, give 6 RBC (1:1 ratio) Group 2 = For every 3 plasma, give 6 RBC (1:2 ratio)
Platelets	As soon as the subject is randomized for a massive transfusion Group 1 = For every container, give 1 dose of platelets (1:1 ratio) Group 2 = For every other container, give 1 dose of platelets (1:2 ratio) *1 platelet dose equal to either 6 random-donor units or 1 apheresis unit

Crystalloid and artificial colloid fluid use is highly variable in clinical practice, largely because Level 1 data are not available to guide their use. Therefore, their use in PROPPR, consistent with a pragmatic trial, will not be standardized or randomized, but their use will be recorded throughout the trial and data collection period to allow for ancillary analyses taking this information into account. The use of pharmacological adjuncts (rFVIIa, amicar, tranexamic acid, PCCs, fibrinogen concentrates, etc) and cryoprecipitate is highly variable in clinical practice, also largely because Level I data are not available to guide their use. Therefore, their use in PROPPR will not be standardized or randomized, but their use will be recorded throughout the trial and data collection period to allow for ancillary analyses taking this information into account. Stratification by site, in the randomization and subsequent analysis with site as a covariate as described in the statistical analysis plan will be used to provide some adjustment for site-related variability in use of the above described products. In ancillary analyses we will adjust for pre-randomization treatments.

Subjects who have re-bleeding events or require MT ***after*** the PROPPR transfusion protocol has been discontinued will be managed per site-specific, laboratory-directed, or institutional guidelines. These products will be recorded in detail until hemostasis is achieved. Re-bleeding requiring arteriogram embolization or unscheduled return to the OR after the PROPPR transfusion protocol is discontinued will be recorded as an adverse event.

Any deviation from these transfusion guidelines will be recorded as such.

5.2.5 Clinical Data Collection

Direct bedside data collection will begin at time of the highest level trauma subject arrives in the ED and will continue until 1) it has been determined that the subject is not eligible for this trial, 2) the subject or LAR refuses continuation in the trial, 3) the subject has achieved hemostasis 4) the subject has expired or 5) 24 hours have elapsed, whichever comes first. Until deemed ineligible, data from subjects will be collected and reviewed for screening purposes. Data on eligibility will be submitted to the HDCC to allow a description of screened versus enrolled subjects.

At screening, in addition to collecting ABC scores, we will collect data for the Trauma Associated Severe Hemorrhage (TASH) Score[64] to allow later comparisons between the two scales (Table 2). The TASH score requires the hemoglobin results and is thus not readily available before randomization needs to occur. By collecting information on both scoring systems in the same patient population, this will allow for a direct comparison between the two methods. Direct bedside data collection will continue on all randomized subjects until 1) active resuscitation has ended , or 2) 24 hours has elapsed. Data to be collected during direct observation will include all blood product transfusion information including the start time of each unit, uncrossmatched vs. crossmatched information, leukoreduced vs. nonleukoreduced products, life saving interventions (LSI), all fluids and blood products, initial clinical laboratory results, surgical procedures and complications. For the purposes of this trial, all fluids and blood products given prior to the randomization process will be documented in the study data collection forms as pre-randomization fluids/products. All fluids and blood products given after the randomized ratios are terminated and prior to 24 hours will be documented as post-randomization fluids/products. The Data Collection Flowsheet (Appendix 3) shows a list of type of data to be collected as well as the frequency of the data collection.

Data will be collected on a daily basis for 30 days of hospitalization or until discharge/death on all subjects who have consented to continue in the trial. Information collected will include demographics, injury, blood product transfusions (including age of products), damage control and other surgical interventions, vital signs, routine daily lab results, complications such as MOF, ALI, TRALI, AKI, ARDS, transfusion-related hyperkalemia and/or hypocalcaemia, all thromboembolic complications (*i.e.*, DVT, PE, MI, stroke), sepsis, abdominal complications, compartment syndromes, and infections. Routine clinical laboratory tests will vary between sites. Common lab tests might include CBC with platelets, electrolyte panel, coagulation tests (PT/PTT/INR), TEGs, fibrinogen, blood type, arterial or venous blood gas, and urinalysis. Available lab results will be recorded. In addition to the information collected daily, the final/discharge diagnosis, discharge destination (i.e. home, long term acute care hospice, skilled facility, death), and discharge extended Glasgow outcome scale (GOSE) will be obtained at the time the subject is discharged from the hospital.

Data will be collected using standardized case report forms. After data collection, the data will be entered into to a secure, web-based data system designed for this trial. The web-based program will provide the flexibility of entering data from multiple locations and centralizes the data management process. To ensure security, each user will be assigned a username and password and this username, date and time of each login will be recorded in a login history file to ensure a record is maintained of each access to the system. This information will also be recorded in the change history audit logs. The data entered for the PROPPR trial will be maintained in a secure database at the HDCC.

If discharge occurs before hospital day 30 and the subject is discharged to a hospice, nursing home or other healthcare provider, research staff will contact the facility to ascertain the subject's vital status. If the subject was discharged to his/her usual residence before day 30, the research staff will contact the subject or their family/legally authorized representative (LAR). If vital status remains unknown the clinical site will request periodic searches for the subject's social security number in the Social Security Master Death Index, the respective State Health Department's vital statistics/mortality database, and the mortality databases of a credit reporting agency, e.g., Experian. For subjects not reported as deceased by these sources by day 30 following ED admission, batch searches of the mortality databases will continue every quarter until trial close-out. Date (and cause of death when available) for out-of-hospital deaths will be documented; however, underlying and contributing causes of death may not be available from these sources. A subject will be considered to be alive if they can be contacted or are reported alive by a healthcare facility, LAR, or other administrative data source at or after the 30-days from admission. Selected elements from the medical records (OR notes, patient history, morbidity and mortality notes, etc.) will be collected in a HIPPA compliant manner and presented to a death adjudication committee for all in-hospital deaths for subjects enrolled in this study. For subjects discharged to another facility, the clinical research staff should complete an authorization form to release protected health information (PHI) and obtain signatures from the subject or LAR prior to discharge. A copy of the signed authorization form and study consent will be provided to the facility for release of PHI. Clinical sites will follow local and state HIPPA guidelines for release of PHI for research.

5.2.6 Research Laboratory Data Collection

Throughout this trial, we will collect blood samples from severely injured subjects upon arrival and sequentially for 72 hours. Plasma will be assayed for coagulation mediators, complement proteins and inflammatory mediators. Functional measures of coagulation and platelet function will be assessed on fresh whole blood. **These samples are for research only and will not be available to inform clinical decisions.** These data will be utilized to develop a systems level characterization of coagulopathy in seriously injured subjects. By comparing functional coagulation and plasma protein measurements with physiologic measures as well as outcome data we will obtain for the first time a complete picture of the timing, severity and causes for early coagulopathy, later inflammation, infection and organ failure after severe trauma and shock.

Blood samples will be collected upon arrival in the ED (time 0) for all screened patients and at 2, 4, 6, 12, 24, 48, and 72 hours (or discharge from hospital – whichever occurs first) for all randomized subjects. The eight time points were selected to provide a broad temporal survey of hemostasis after injury, which is weighted toward early sampling to fully characterize the early phase of TIC. Later sampling (48 and 72 hours) will allow us to characterize the transition from a hypocoagulable to a hypercoaguable state and to fully examine the effect on resuscitation and outcome on coagulation and inflammation after injury and shock. All attempts will be made to obtain study samples at the designated time intervals. All research samples must be collected within +/- 30 minutes. In the event that samples cannot be collected in this time frame, documentation will be noted on the data collection forms.Only the 0 hour sample will be collected and processed for those subjects who are screened, determined to be eligible (at the 0 hour blood draw) but are not randomized. The 0 hour samples collected on the screened patients will be processed and stored for future analysis. The analysis will include coagulation mediators, complement proteins and inflammatory mediators similar to the serial samples collected on the enrolled subjects. The analysis will not include any genetic analysis. These 0 hour samples will also be identified by a study code number. A modified consent process will be conducted in this group of subjects. The method of consent (i.e. waiver of consent, waiver of documentation, or full consent) will be dependent on the site's local IRB policies and regulations.

Up to 23 ml of blood will be collected in addition to the clinical sampling at each time point into multiple different tubes. The blood volumes collected for research purposes are below IRB recommended 3-5% total blood volume within 24 hours. The sampling tubes will include 1) 1 citrate for for whole blood analyses, 2) 2 citrate for plasma, 3) Blood Collection Tubes 1 citrate plus a protease inhibitor for special assys and 4) 1 blood collection tube with EDTA and cell preservative for flow cytometry analyses. Samples will be collected by the clinical person responsible for implementing physician orders for laboratory testing. The clinical research staff will then be responsible for the processing and shipping at each site. All samples drawn for research purposes will be identified by the study number, the site identification number and date/time of collection. No personal identifying information will be included on the samples processed for research purposes. Assays that require immediate processing (TEG, Multiplate) will be performed at each study site by personnel trained at the core lab sites or send by an overnight courier to the central flow cytometry lab (UTHealth) for analyses. Other samples will be spun, aliquotted, frozen at -80°C, bar coded, and batch shipped by the clinical research staff to the appropriate labs (UTHealth, UCSF, and Vermont) for measurement. The samples will be disposed per appropriate biohazard guidelines.

The research laboratory data will be entered into a web based relational database created for the lab measurement component of this trial.

6. STUDY OUTCOME MEASURES

6.1 Primary Clinical Outcomes

Absolute percent (rather than relative percent) group difference in 24-hour and 30-day mortality (Separate co-primary outcomes)

Rationale for the Co-Primary Outcomes (24-hour and 30-day mortality)

Despite a consensus conference on outcomes for blood product studies, disagreement remains; thus, we chose co-primary outcomes. The two outcomes will be considered as separate study questions and both outcomes will be reported in the initial report on the PROPPR trial.

Rationale for 24-Hour Mortality: In PROMMTT, the recently completed, ten-center observational study, 297observed patients received a massive transfusion (MT). Of the 297 observed MT patients, 117 (39%) died in-hospital within 30 days of ED admission. Of those 117 in-hospital MT deaths, 83 (71%) occurred within 24 hours of ED admission across all blood ratio groups combined. The potential benefit of transfusing optimum blood product ratios to severely injured trauma patients soon after ED admission, and reducing or preventing coagulopathy altogether will be most easily detectable after ED admission within the brief 24 hour span of highest mortality risk. Deaths among trauma patients within the first 24 hours are more often due to massive bleeding that is amenable to rapid resuscitation with an appropriate transfusion protocol than deaths occurring later in the course of an extended 30-day hospitalization that may be unrelated to the transfusion protocol.[75]

Recent meetings on optimal endpoints in randomized trauma studies (February 2008, Dallas, TX & September 2009, Houston, TX) included multidisciplinary injury experts from academia, Department of Defense (DoD), industry, FDA, and academic societies. Furthermore, the PROPPR trial design was reviewed at the recently held State of the Science Transfusion meeting jointly sponsored by NHLBI and DoD.[76] The conclusion from these three meetings was that the primary outcome of future trauma trials, including PROPPR, should be 24-hour mortality reflecting the changing epidemiology of trauma.[77] Based on the time to death in recent military and civilian studies, and agreement from experts in the field, 24-hour mortality will be the co-primary outcome of the PROPPR trial.

Rationale for 30-Day Mortality: In PROMMTT, of the 117 in-hospital MT deaths, 98.7% of these deaths occurred within 30-days. PROPPR will use 30-day mortality as a co-primary outcome as the latter is a traditional trauma trial standard for evaluating delayed complications and safety of trial interventions, the benefit is durable, the outcome is important to scientists and patients and provides evidence to support the most efficient use of the nation's blood supply. All PROPPR subjects will be tracked for vital statistics for a full 30 days, whether or not they have left the hospital.

Both the 30-day and 24-hour mortality outcomes will be reported on all publications and reports that arise from the data collected in this trial.

6.2 Ancillary Clinical Outcomes

Time to hemostasis hospital-free days, ventilator-free days, ICU-free days within the first 30 days or hospital discharge, whichever comes first); incidence of major surgical procedures (e.g., thoracotomy, craniotomy, laparotomy, major amputation), complications (transfusion-related acute lung injury, acute lung injury, acute kidney infection, multiple organ failure, acute respiratory distress syndrome, sepsis, abdominal complications, infections, thromboembolic complications, rebleeding requiring an arteriogram or unscheduled return to the OR after PROPPR transfusion protocol discontinuation, transfusion-related hyperkalemia and/or hypocalcaemia during hospitalization), the number and type of blood products used from randomization until hemostatsis is achieved, the number and type of blood products used after hemostasis is achieved to 24 hours post-admission and functional status at hospital discharge or 30 days, whichever comes first, as measured by discharge destination and GOSE.

Rationale for Ancillary Clinical Outcomes

These comparisons will allow assessment of other possible benefits and complications related to treatment (ratio) group. Also these data will be important in developing the models describe in 6.3 below.

6.3 Primary Research Laboratory Outcomes

Models will be developed to identify drivers and sequelae of TIC and inflammation, and to characterize the natural history of the coagulation milieu. The principal modeling approach will be reverse-engineering of the biological networks from the research laboratory data augmented by the existing expert knowledge. Both baseline (Laboratory Aim 1) and dynamic (Laboratory Aim 2) models will be developed. When interpreting the resulting models (Laboratory Aim 3), special emphasis will be put on the primary and ancillary clinical outcome measures for laboratory analyses, including mortality, time to hemostasis, incidence of coagulation abnormalities, total blood product transfusions, incidence of organ injury (i.e., acute lung injury and acute renal failure) and ventilator associated pneumonia, 30-day mortality, ventilator-free, ICU-free and hospital-free days and incidence of nosocomial infections.

7. PROJECTED ENROLLMENT

7.1 Availability of Study Population for Phase III trial

Based on unpublished data from the retrospective study and PROMMTT, the total number of subjects actually receiving MTs during the Vanguard stage data collection period (6 months) for at least 4 centers is expected to be 80 (an average of 40 MT subjects per site/per 6 months). Based on an analysis of the retrospective data using the ABC prediction algorithm,[61] the Vanguard stage is planned to randomize at least 60 subjects predicted to receive MTs over the 6 month data collection period. Only 50 of the 60 (80%) subjects randomized are expected to actually receive a MT within 24 hours of admission.

7.2 Timeline for the Phase III trial

As a conservative estimate based upon the data from our site selection surveys, we expect to enroll at least 2.7 patients per site per month. Using 12 sites that initiate enrollment at a staggered rate as they complete their public notification community consultations, we project that we will enroll the required 580 patients within 24 months.

PROPPR Timeline *Based on ROC fiscal year (January 1 – December 31) and budget.*					
Activities	**Period 1 10/10-12/10**	**Period 2 1/11-12/11**	**Period 3 1/12-12/12**	**Period 4 1/13-12/13**	**Period 5 1/14-9-14**
Planning	✓	✓			
Site Training		✓	✓		
IRB approval/Community Consultation		✓	✓		
Enrollment			✓	✓	✓
Follow-up to 30 days			✓	✓	✓
Trial Monitoring			✓	✓	✓
On-going Data Analysis			✓	✓	✓
Trial Close-out					✓
Sample Collection/Lab Analysis			✓	✓	✓

7.3 Sample Size for the Phase III trial

At the DSMB meeting, April 25, 2013, prior to any review of unblinded data the blinded members of the DSMB reviewed a prespecified adaptive analysis conducted by blindied ROC biostatisticians and recommended that the sample size be increased from 580 to 680 to maintain a power of >85%. NHLBI approved this modification.

Primary Outcomes:

24-hour mortality

For sample size estimation for the 24-hour mortality outcome, we chose a difference of 10% or greater increase in mortality from 11% at 24 hours to 21% when comparing 1:1:1 to 1:1:2. The trial is powered at 90%, with a two-sided alpha level of 0.05, adjusted for interim analyses to 0.044.[78] The required sample size is 580 subjects including subjects from the Vanguard stage.[79-83] The 1:1:1 group mortality of 11% was selected based on a subset of published data available from a retrospective study showing 115 predicted MT patients had received 1:1:1 ratios and experienced an 11% mortality at 24 hours.[49] In contrast, 24 hour mortality was 41% in the 27 predicted MT patients receiving 1:1:2 ratios. We considered a between group difference in 24 hour mortality of 10% or greater to be clinically meaningful and of sufficient magnitude to influence clinical practice. Adjusting for site generally should increase power unless there is a lack of homogeneity of treatment effects across sites.

PROMMTT Effect Size Estimates for PROPPR

PROMMTT was a prospective observational study. To reduce survival bias as much as possible while allowing for individual variation in patients' cumulative blood product ratios over the 24 hour period following Emergency Department (ED) admission, we used Cox proportional hazards modeling with time-dependent covariates for the ratios (i.e., plasma:RBC and platelet:RBC ratios were treated separately). Cumulative ratios were re-computed for every half-hour interval through hour 6, and the cumulative ratios at hour 6 was re-applied to the last interval, >6-24 hours following ED admission. Vital status was recorded and survival time was computed for each patient over all the time intervals. Our analyses avoided subgroup analyses using the standard definition of massive transfusion (MT) due to concerns that the MT subgroup would 1) exclude many of the eligible and hemorrhaging patients expected to be enrolled into PROPPR (i.e., those who will die or receive interventions that control bleeding with no chance for a 10th RBC transfusion within 24 hours of ED admission), and 2) contribute to survival bias. We developed, *a priori*, an alternate subgroup definition free of survival bias to encompass the population of substantially bleeding (SB) trauma patients likely to be enrolled in PROPPR. The subgroup of SB patients was defined as follows: receipt of the first RBC transfusion within 2 hours of ED admission, either death or continuing RBC transfusions < 2 hours apart, and within 4 hours of ED admission, at least 5 RBC transfusions or death following 1-4 transfusions.

The hazard ratio (HR) estimates for the association of 24 hour mortality with plasma and platelet:RBC transfusion ratios in the SB subgroup of PROMMTT patients suggest an overall 0.60 relative risk estimate. This was computed from a 0.78 HR for the 1:1 vs 1:2 plasma:RBC ratios X a 0.77 HR for the 1:1 vs 1:2 platelet:RBC ratios = 0.6006, the HR for the joint association between 1:1:1 vs 1:1:2 plasma:platelet:RBC ratios and mortality within 24 hours of admission to the ED. These HRs were adjusted for potential confounding by center and patient characteristics including the number of units of RBCs received, age and Glasgow Coma scores.

Results from PROMMTT (Table 5) may not directly predict achievable effect sizes for the randomized PROPPR trial because PROPPR is testing blood product ratios that are fixed from the point of randomization, not varying over time. Nevertheless, a range of expected effect sizes has been estimated in the table below by applying adjusted[84] relative risk estimates (from the HR estimates) to the 24 hour mortality rate observed in the subgroup of PROMMTT patients with substantial bleeding, under 3 different assumptions. The adjustment provides more conservative estimates (relative risk estimates closer to the null of 1.0) than the HRs and a reasonable range of possible effect sizes for the 1:1:1 vs 1:1:2 transfusion ratio comparisons, to the extent that PROPPR can be expected to map onto PROMMTT.

Table 5. Estimated PROPPR 24 Hour Mortality Rates and Effect Size Estimates Applying Adjusted[84] Relative Risk Estimates from PROMMTT Hazard Ratios for the Subgroup of Substantially Bleeding Patients

Assumptions for PROMMTT Mortality Rate	1:1:2 Group	1:1:1 Group	Absolute Difference (Effect Size)	Estimated Statistical Power*
If PROMMTT rate applies to PROPPR 1:1:2 group Adjusted RR=0.6438	29.2%	18.8%	10.4%	82.2%
If combined groups sum to the PROMMTT rate, assuming a 50:50 split Adjusted RR = 0.6576	35.2%	23.1%	12.1%	88.5%
If PROMMTT rate applies to 1:1:1 group Adjusted RR=0.6791	43.0%	29.2%	13.8%	92.8%

*Assuming a 0.044 alpha level, two-sided Mantel Haenszel test, 580 total patients

30-day mortality

For the 30-day mortality, a 12% or greater difference in mortality from 23% in the 1:1:1 group is detectable given the same sample size (580), with 88% power, and a 10% or greater difference is detectable with 74% power assuming a 2-sided alpha of 0.044. The primary group of interest, 1:1:1, mortality was based on additional unpublished retrospective data as described for the primary outcome. Subjects in PROMMTT were followed only to hospital discharge, not 30 days. Adjusting for site should generally increase power unless there is a lack of homogeneity of treatment effects across sites.

Ancillary Clinical Outcomes

We will compare treatment groups on a variety of ancillary outcomes as listed in 6.2. For binary outcomes we can detect an absolute difference of 12% in outcomes from 50% (worst case scenario) with power of 80%, 2-sided alpha of 0.05, given a sample size of 290 per group. If some outcomes are rare as we expect, we can detect a difference from 0.03 of 0.029 with same power and alpha. For continuous outcomes, we can detect an effect size of as small as 0.233, a very small effect as defined by Cohen[85] for behavioral sciences at same alpha and power.

Laboratory Modeling

Because no previous prospective and comprehensive characterization of coagulopathy and inflammation after trauma currently exists, and the definitions of phenotypes of primary interest, while suggested by preliminary data (elevated INR, activation of anticoagulant pathways, dilution, hypothermia, etc.) are not codified, we expect to use the entire cohort of 580 for the systems biology (exploratory) analyses. This is predominantly a multivariate modeling approach

that is aimed at hypothesis generation rather than hypothesis testing. Due to the non-parametric nature of the corresponding analysis methodology (e.g., dynamic Bayesian networks, ensemble classification algorithms), it would be impossible to carry out a straightforward power analysis. Given the exploratory nature of this aim, we cannot determine the exact dimensionality and size of the models that may emerge. However, if we limit ourselves to the immediate Markov neighborhoods of the primary and secondary laboratory research outcome variables (i.e., perform automated variable selection), the dimensionality of the resulting sub-networks should be favorable for the purposes of model validation (using resampling techniques such as bootstrapping) and subsequent predictive modeling (Laboratory Aim 3).

Once phenotypes and relationships are identified, we will use more traditional statistical analyses to assess impact of the phenotypes and interactions among the phenotypes on outcomes. Based on work by Harrell with 580 subjects, depending on the final model chosen, we can build linear regression models that include up to 58 variables where outcome is continuous (amount of blood products, etc.), and logistic regression models that include up to six variables where the outcome is binary (mortality, MOF, etc).[86-88] If the number of variables exceeds the number that can be included in a linear or logistic model we will prescreen using a p value of <0.25 to select the subset to include in the model. We may need to conduct separate analyses of the selected phenotypes depending on the number of baseline covariates of interest. This serious limitation of traditional statistical approaches emphasizes the need for the initial more complex approaches to understanding coagulapathy and inflammation as described in the analysis below.

8. ANALYSIS PLAN

8.1 Vanguard Stage

Assessment of Trial Feasibility

Once at least four sites are eligible to enroll subjects we will begin a Vanguard Phase to assess sites' abilities to recruit subjects and comply with the protocol. These early data will be used to assess trial procedures and feasibility. We will descriptively (graphically) compare the hypothesized timeline for recruitment to the observed time line for recruitment and to the NHLBI target range (ref). We will also collect the following site performance metrics of protocol compliance:

- Protocol deviations (both self-reported and study monitor evaluation)
- Time to blood product container delivery
- Time to complete enrollment
- Missed/unable to screen subjects
- Volume of data queries
- Evaluation of source documents and CRFs (study monitor site reports)
- Site response time (timely data entry, submission of regulatory documents)
- Adverse events management
- Site lab adherence to lab sampling process (processing/shipping errors)

We will complete analyses of data quality including missing data, error patterns, protocol violations, etc. to determine if modifications in the protocol or data collection procedures or trial manual of operations are needed or to determine if the protocol itself can be followed. The DSMB will review blinded data on recruitment, protocol deviations, laboratory data, data quality and adherence to study procedures, including a count of the number of instances when patients were not randomized, based on physician judgment in the presense of a positive ABC score (physician override). At the end of the Vanguard phase, the DSMB will develop recommendations for NHLBI to continue with the trial without modification, continue with modification including possible termination of a site or sites, or to discontinue the trial based on the inability to follow the protocol. The DSMB will determine if the Vanguard data can be included in final trial data set. This DSMB review will be in addition to the ongoing DSMB safety review completed each time the DSMB meets as described in Section 8.2.5 below. Regular blinded monitoring and quarterly reports will be submitted to the HCCC and Clinical Sites to maintain a constant focus on data quality.

8.2 Trial Analysis

8.2.1 Primary Clinical Outcomes

Analyses for each of the separate Phase III trial co-primary outcomes (24-hour and 30-day mortality) will be intent-to-treat. We will include all subjects in all primary analyses in the Phase III trial as randomized. We will compute mortality at both 24 hours and 30 days. For subjects who have not been reported as deceased by day 30 following ED admission from any of the sources queried we will use multiple imputation under the assumption that the missing data are not missing at random. The process for determining whether or not a subject is deceased at 30 days is described in detail in section 5.2.5. We will make extensive efforts to capture all data and anticipate less than a 10% of the subjects will be missing vital statistics at the 30 day co-primary outcome. The DSMB will be informed of the amount of missingness observed, will carefully monitor the amount of loss to follow-up throughout the trial and will call for further corrective actions or changes to the protocol in an effort to keep the value less than 10%.

We will analyze each of the 24-hour and 30-day mortality endpoints as a fixed point in time using a two-sided Mantel-Haenszel (M-H) test taking site, the stratifying variable, into account. This approach has more power than the survival analysis described below given the potential for crossing hazard functions.[89] We will also test homogeneity of the odds ratios across sites using the Breslow-Day test. The M-H test is robust to lack of homogeneity of odds ratio although power would be reduced. We will compute 95% confidence intervals on mortality by treatment group at 24 hours and 30 days. We will also conduct a sensitivity analysis of 30 day mortality to assess the effect of imputation as alive on the treatment group comparisons and confidence limits for the 30 day outcome.

To provide further insight we will compute 30-day Kaplan-Meier survival curves.[90] We will use Cox proportional hazards regression to take site (as a random effect) into account.[91, 92] If the proportional hazards assumption is violated we will include a time treatment interaction in the model and choose the appropriate approach.[93] As an additional analysis, we will use the same Cox proportional hazards approach to adjust for baseline covariates such as age, gender, admission blood pressure and GCS, type and extent of injury, amount of pre-randomization blood products and other treatments received, time to randomization. Since site is a stratifying variable site will be included as a random effect. We will do pre-screening of covariants other than site at the 0.20 level before fitting the final model if our sample size is not sufficient to include all covariates in the model. We would follow the approach above to test for and take crossing hazards into account if applicable. As an additional exploratory analysis we will compare 30-day survival in the two groups adjusting for the covariates listed above and any additional baseline covariates that are imbalanced between treatment groups ($p<0.10$) using the same screening approach to decrease the number of covariates included in the model, if necessary.

8.2.2 Analysis of Ancillary Clinical Outcomes

Unless there is sufficient power (predetermined before the analysis is begun) the approach to ancillary analysis will generally be the calculation of confidence limits on intervention group differences or model parameters rather than formal tests of significance at a specified critical level as the trial will not have high power to detect difference in all of these outcomes. However, these comparisons will add to the knowledge of the benefits and risks of the two interventions.

8.2.3 Analysis of Research Laboratory Data

A systems level framework is necessary to produce predictive models capable of diagnosing coagulopathic phenotypes and assessing the effectiveness of hemostatic resuscitation measures. Our goal is to develop an *in silico* model of coagulation to better understand the perturbations of this system after trauma. To accomplish this goal we will both expand our existing coagulation network model, and construct new network models of Protein C, complement, and coagulation in general from our PROMMTT and legacy data, as well as data from the measurements and clinical data in the PROPPR trial. Specifically, we will scrutinize the sub-networks representing structure/ function relationships of protein C and coagulation, and their interactions after injury.

Our analysis is divided into two overlapping modeling goals: A) building a network and functional model of coagulation (Laboratory Aims 1 and 2) and B) predictive modeling (Laboratory Aim 3), using predominantly machine learning methodology. Each is distinct but complimentary and serves to inform the other model (for

example, the latter would provide additional insights on the variable selection for the former). Ultimately our descriptive and predictive modeling efforts will involve the following steps and methods:

1. Network Expansion and Construction. We will begin by expanding our existing preliminary network model of coagulation to include all links to all known nodes up to 5 degrees away (i.e., in the extended Markov neighborhood) from protein C and proteins included in the classical coagulation cascade and complement system. Additional network proteins will be added to a network spreadsheet and imported into Matlab™ Pajek 1.8 (The Mathworks, Inc., Natick, MA) and Cytoscape 2.0 (Cytoscape Consortium, San Diego, CA) bioinformatic network software for visualization and analysis. This is a methodologically straightforward step that will lead to the creation of baseline networks (Laboratory Aim 1).

2. Network Analysis. Topological calculations of degree, degree exponent γ (where $P(k)\sim k^{\gamma}$, path length, cluster coefficient of each node ($C_i=2n_1/k(k-1)$), average cluster coefficient ($C(k)\sim k^{-1}$) and edge-betweenness (cluster decomposition) will be calculated with Cytoscape 2.0 and Guess.5 and Matlab™. Network topology will be mapped onto outcomes including coagulopathy, and infection. In this manner we will test the relation between perturbations in topology with the outcome of coagulopathy and infection. Again, this is a computationally straightforward step that will result in developing reference networks relevant to the Laboratory Aims 1 and 2.

3. Dynamic and Data-driven Model(s) Construction. We will next construct dynamic network (ordinary differential equation and dynamic Bayesian networks - based) models of the central coagulation system and its relationship to inflammation in general.[94-96] These will serve as starting points (topology priors) for accomplishing Laboratory Aim 2 --- we will follow up by reverse-engineering (using our proprietary Bayesian network modeling software [97]) data-driven network models from a subset of data from this project, the currently ongoing PROMMTT study, and protein C activation data from both steady-state (non-injured) and perturbed (injured) conditions. This cumulative model-refining process will continue as new experimental data are collected and new hypotheses are developed.

4. Variable Importance Analysis. In a parallel line of research to the biological network modeling above we will be creating statistical and computer science – based models (classifiers) to support treatment decision for optimal outcome given clinical observations. Due to the large number of clinical, physiological, and molecular variables we are proposing to collect, a necessary first step is determining which of these, by themselves or in concert, are most important to outcome, a task known as "variable selection".[98, 99] We will pursue various variable selection strategies that take into account variable interactions, including the Bayesian network Markov neighborhood analysis, ensemble decision tree classifiers and other (mostly machine learning) methods.[100, 101] This analysis is directly relevant to the Laboratory Aim 3, but will also retrospectively influence our network modeling activities (Laboratory Aims 1 and 2)

5. Clinical Prediction Analysis. The next goal is to define statistical or computer science-based predictive models that can be used to identify subjects at high risk of a clinical outcome [102].We will use machine learning techniques (ensemble decision tree classifiers, support vector machine classifiers and possibly naïve Bayesian classifiers) to find predictors with high specificity and sensitivity. From our experience, as well as from the recent literature, we expect these techniques to perform better (in terms of generalization classification accuracy, robustness and scalability) than the more traditional regression methods. We will finalize our analyses by using a Superlearning approach.[103] This approach expands the typical machine learning classification algorithms to construct final predictive models that are combinations of several machine learning classifiers, thus avoiding possible method-related biases, and guaranteeing substantially improved robustness In addition to the complex systems analyses that would be conducted, we will also use more traditional statistical models for Laboratory Aim 3, incorporating phenotypes and interactions identified in Analysis #4 above. Linear models would be used for Laboratory Aim 3 to test the association between identified phenotypes and outcomes that are continuous (amount of blood products, etc) and logistic models to test associations with categorical outcomes (MOF, etc). These analyses will take appropriate baseline covariates and treatment group into account to assess the effect of the phenotypes beyond the effect of these covariates. This will accomplish Laboratory Aim 3.

6. Model Validation. We will use statistical resampling approaches (bootstrapping, dataset subdivision and cross-validation) to provide model validation. Taken together, our data and models will result in the first comprehensive natural history description of acute traumatic coagulopathy.

Our modeling goals are ambitious but both types of models lead to predictions that will be clinically tested. The results will themselves inform the second generation of models (thus going back from the Laboratory Aim 3 to Aims 1 and 2). This is one of the key strengths of this program—the tight coupling of clinician to analyst, sometimes in the same person. The project itself will adhere to a tight management scheme in which the teams meet around the continuously updated models to discuss their completeness and their descriptive and predictive accuracy. The models will, therefore, also serve as precise communication tools for the project scientists. Ultimately these models will identify a group of mediators that define coagulopathic phenotypes after trauma, and can be used to guide personalized medical and surgical treatment for wounded patients.

8.2.4 Missing Data

We expect no missing data for 24-hour mortality. For 30-day mortality, given the transient nature of many of the subjects, extensive efforts will be made to ascertain vital status (Data Collection section 5.2.5 above). Batch searches of the mortality databases will continue every quarter for subjects with unknown status, until trial closeout. For interim and final analyses, of subjects who have not been reported as alive or deceased by day 30 following ED admission from any of these sources we will use multiple imputation for the final value assuming missing not at random (MNAR). As sensitivity analyses we will report the data with and without imputation. We also report a secondary analysis consistent with that used in other trauma studies counting those missing as alive on day 30.

8.2.5 Monitoring for Effectiveness & Safety

Adaptive Design: At the time of the first interim analysis but before presentation of the interim analysis to the DSMB per FDA guidelines for adaptive designs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm201790.pdf) a blinded biostatistician from the ROC DCC will report on the power for the trial based on the observed 24 hour mortality rate in the 1:1:1 group (the comparator arm) only. If the mortality rate in the 1:1:1 arm is less than 11%, there is no need to consider an adjustment to the sample size as power to detect a 10% difference from 1:1:2 would be increased. If the mortality rate in the comparator arm is greater than 11% we will ask the DSMB to consider increasing the sample size to an amount to be determined by the difference between the comparator group rate and a clinically meaningful difference of 10%, two-sided alpha = 0.05, power = 90%. The DSMB would not be provided and would not consider the observed difference between the two treatment arms at this time. The DSMB will then make a recommendation to NHLBI to maintain the sample size as planned, or to increase the sample size a specified amount based on the observed mortality in the 1:1:1 group. Final determination of the amount of the increase in sample size will be made by NHLBI based on availability of funds and based on recruitment progress to date, protocol adherence, and data quality but without any knowledge of the observed treatment group differences. Once this recommendation is made, the DSMB would then proceed with its regular meeting reviewing the interim analysis and safety analysis. This later discussion could, of course, change the recommendation if a decision was made to recommend trial termination for reasons of safety. No further consideration of a sample size increase would be made once the DSMB has seen the interim analysis.

Interim analyses for Effectiveness: There will be three formal effectiveness analyses. The two interim analyses for the DSMB will occur after the first 1/3 and 2/3 the projected 24-hour or 30-day mortality events are observed (whichever reaches its projected 1/3 and 2/3 first). The two co-primary outcomes will be separately monitored using a two-sided O'Brien-Fleming boundary with Lan-DeMets alpha spending function based on events for each of the two comparisons.[32] The boundary is suggested as a guideline for the DSMB, and could be modified by the DSMB prior to the start of the trial. Other information could influence their decision to recommend continuing (or stopping) the trial in the face of a clear difference in either direction between treatment arms.

If the trial stops early because of interim analysis, we will report the adjusted p-values by using the stage wise ordering approach to account for the fact that an unadjusted p-value will tend to overstate the evidence against the null hypothesis in sequential trials.[104]

We will not test for lack of a difference in effectiveness using a stochastic curtailment approach since the null hypothesis is also of clinical interest for both co-primary outcomes. If we cannot detect a difference between groups, we would want to use the full sample size to produce narrow and informative confidence intervals.

Safety analyses
At each DSMB meeting after the start of the trial we will present safety data by treatment group (labeled as A, B in the same manner proposed by the 2006 FDA Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committes, unless the DSMB requires complete unblinding). This would include, but is not limited to, total counts of all serious adverse events, both unanticipated and anticipated, including a description of the event itself. Additional safety analyses will be developed as requested by the DSMB. We will report overall mortality but will only report mortality by treatment group (or A,B) at the formal interim analyses as these are the primary outcomes. After completion of the Vanguard phase, we will also continue to present process monitoring data to the DSMB (recruitment, data quality, etc.).

9. DATA MANAGEMENT

The subjects will be identified by a study number only. All hard copy source documentation will be kept in a secured, locked cabinet in the site‘s research coordinator‘s office. All study documents will be maintained in a secure location for two years following study completion unless superceded by participating site‘s requirements. The electronic data will be entered and maintained on a password protected web-based program designed for this trial.

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

9.1 Error Checking

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Checks will be developed by both clinical and laboratory investigators. Depending on the question, any item found that does not meet the respective edit criteria will have an appropriate error message displayed when the user tries to save the data. Errors will be classified as either “hard” errors meaning that a valid response is required before the data can be saved or as “soft” errors in which the entry operator can either correct the errors or override them to indicate that the data are correct although it does not meet the edit criteria. Examples of hard errors would be items such as identifiers and event dates. An example of a soft error would be values that are outside a pre-defined range. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are currently four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors. For the first status, the entry user will have the option to save a record as “incomplete” for situations where they have partially entered a form and must stop because of an interruption. This will allow the user or the study coordinator to pull up the form at a later time and finish completing it. If the form was entered without any errors, then the record will be saved as complete. If the user overrides any soft errors found, the record will be saved as “saved with errors”. Staff in the HDCC will have web-access to listings of subject specific errors needing correction by site. These errors can be corrected at the site or in the offices of the HDCC (given documentation of the change). All site investigators will be trained to follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once a follow-up about any errors has been done by the HDCC and the error has been corrected or certified as accurate, the status will be change to “complete with errors.” Once a record has been saved by the site or HDCC as complete, they will no longer be allowed to make changes to the records. Any changes that result from obtaining new information would be made by the staff at the

HDCC. At the end of the trial after all possible corrections are made, the database will be locked and further changes will not be made.

9.2 Error Correction Follow-ups

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

9.3 Investigator Resources and Reporting

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

9.4 Archiving the Final Dataset for Public Use

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

10. QUALITY ASSURANCE

10.1 Training:

Training of research staff and nurses who will be responsible for recruitment and randomization of subjects is planned for the PROPPR study and in line with standard ROC procedures. A standard manual of operations developed by the HCCC and HDCC's research teams will provide standard definitions of all study variables (i.e., data elements) and describe all data collection and data entry procedures in detail. Copies of the manual will be distributed to all Consortium sites to be used in training each site's research team and will be available on the study website through the HDCC section of the ROC website. In addition to the planned training meetings, each site will be responsible for the complete education of their personnel in the conduct of the PROPPR study.

10.2 Laboratory Quality Assurance

All laboratory samples collected for research purposes for the PROPPR trial will be sent to the PROPPR Core Research Laboratory that is located on the 5th floor of the Medical School at UTHealth. Where certain assays require specific equipment or expertise, laboratory samples will be shipped from the core laboratory at UTHealth to specific research laboratories such as UCSF (Cohen) and the University of Vermont (Mann). A standard quality assurance process will be in place for every research laboratory test. Where the a research laboratory does not have a standard quality assurance process in place, a system for sending split samples for reanalysis (where possible) will be put into place. The strict quality control ethic of the core laboratory is a reflection of its personnel and has evolved from methodology that has been in place for many years and improved upon by the vast experience of the collaborators in large, inter-disciplinary studies. A list of quality control measures include: maintaining proper sample identification and storage, preventing contamination, inventory organization and database management and monitoring and maintenance of equipment and its performance. Importantly, standardized calibrated material will be used on a regular basis at all testing sites to validate both methods and performance.

10.3 Study Monitors

The study monitors will report to both the HCCC and HDCC. Monitors will be trained in trial procedures, trained to identify source documentation, to assess regulatory compliance, to review source documents for agreement with study records, to identify possible unreported adverse events, and to look for protocol violations. The study monitors will review subject medical records onsite only for the purpose of verifying research data as required by law. Each site will be visited by study monitors from the HDCC to certify that the site is ready to begin the trial and will be visited again a few months after the trial begins, if the site has been enrolling subjects. In addition, NHLBI and/or ROC DCC is expected to send representatives annually unless a problem is noted the study monitors.

10.4 ROC Processes for Generation, Evaluation, and Implementation of Protocols

ROC has developed a detailed process for generation, evaluation, implementation, and monitoring of protocols, which PROPPR is following. The PROPPR protocol is a ROC protocol, and once the protocol is approved by ROC, the NHLBI DSMB, the FDA, Health Canada, and site IRBs/REBs, the ROC process includes ongoing protocol review of trial progress by the NHLBI DSMB as well as by the ROC Management, Trauma and Executive Committees. In addition to the active site monitoring by the HDCC, site performance will be monitored by the ROC Study Monitoring Committee. Detailed functions of all the above can be found on the ROC website https://roc.uwctc.org/tiki/tiki-index.php. The FDA, Health Canada and local IRBs/REBs provide additional regulatory oversight. The FDA and Health Canada requires an investigational new drug application because the PROPPR protocol operates under exception from informed consent.

11. ADMINISTRATIVE STRUCTURE

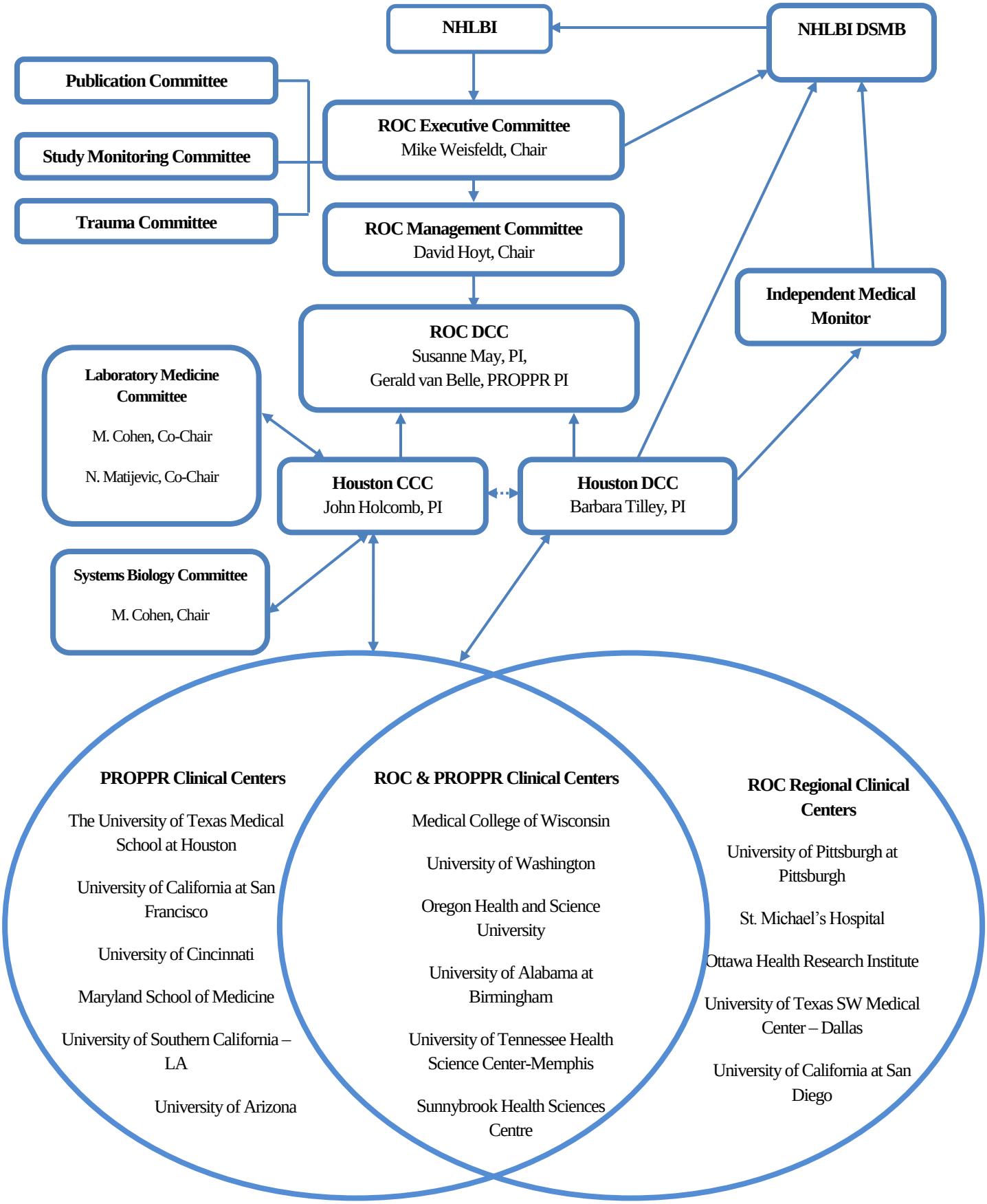
The HCCC and the HDCC are functioning as satellites in the ROC under separate sub-contracts. The HCCC and HDCC conduct the sub-contracts in accord with ROC governing procedures and NHLBI and FDA policies and guidelines. Figure 8 describes the organization structure for the PROPPR trial.

The PROPPR study is one of eight studies currently being conducted by the Resuscitation Outcomes Consortium (ROC). The ROC Data Coordinating Center (DCC) is responsible for clinical and data coordination for all ROC studies and is under the direction of Dr. Susanne May. Dr. van Belle is the Principal Investigator for the ROC PROPPR study. The UTHealth Clinical Coordinating Center (HCCC) and the UTHealth Data Coordinating Center (HDCC) are satellites of the ROC DCC for purposes of the PROPPR trial with the majority of the work being carried out by these satellites. The HCCC will oversee all clinical sites and the laboratory committee. The HDCC will perform data collection activities. Over the last six years, ROC has developed a detailed process for generation, evaluation, implementation, and monitoring of protocols, via several committees, all of which PROPPR is following. Once the protocol is approved by the NHLBI review committee, FDA, and local IRBs/REBs, the ROC quality assurance process includes ongoing protocol review of trial progress by the NHLBI DSMB as well as by the ROC Management, Trauma, Executive and Study Monitoring Committees.

To foster collaboration key personnel from the ROC DCC and HCCC and HDCC will meet on a regular basis. Two of the four meetings of the PROPPR investigators will overlap the semi-annual meetings for all ROC investigators. In addition, ROC DCC personnel communicate regularly with the HCCC and HDCC and will take part in site visits to satellite sites. PROPPR progress will be reported routinely at Trauma, Management and Executive Committee calls.

In addition, we have established the two committees (Laboratory and Systems Biology) and three subcommittees (Emergency Medicine, Anesthesiology, Transfusion Medicine) to assist with protocol administration and compliance.

Figure 8. PROPPR Organizational Structure



12. HUMAN SUBJECTS RESEARCH

12.1 Risks to Subjects

This study will randomize a total of680 subjects in the Phase III trial who have sustained a major traumatic injury and are predicted to receive a MT. The Vanguard stage of this study will involve enrollment of subjects in at least four of the sites for up to a six month period of time. Based on past data, the majority of traumatic injuries occur in male subjects 45 years of age and younger. The majority of this population will have no significant pre-existing medical history. Children estimated to be less than 15 years of age, women who are known to be pregnant, and prisoners will be excluded from this trial. As all products used in this trial are approved by the AABB,FDA, and Health Canada and used in amounts currently in use across trauma centers, we anticipate no new risks to those seriously injured trauma patients. Subjects randomized will receive blood product ratios equivalent to ratios predominantly used at the Level I trauma centers in PROMMTT. See Figures 5 in Section 4.

12.2 Source of Data Collection

Data will be collected prospectively during the trial. This will include a daily review of the medical records and results of diagnostic studies. A description of the data collection process is detailed in section 5.2.5.

12.3 Potential Risks

Eligible subjects for this trial will have been identified as requiring multiple units of blood products due to their traumatic injury. There is a potential risk that products may be delayed due to the randomization process, however all participating sites will have plasma and RBCs rapidly available in the ED for use until the container with the randomized products is available. To monitor the potential risk, the clinical research staff will document relevant times including: time of ED admission, time of randomization, time MT called to the blood bank, and time study container delivered to bedside from the blood bank. If a delay or risk is identified, appropriate information/data will be sent to the DSMB to decide if further action needs to be taken.

Severely injured subjects who receive blood products will frequently incur complications such as death, multi-organ failure (MOF), respiratory complications, and infections. While there is no expectation of harm between groups, the risk of transfusion-related acute lung injury (TRALI) is increased as plasma and platelets use increases, however, most authors place this as a 1:10,000 rate, and this rate must be placed in the context of significantly decreased mortality reported in many recent publications.[25, 66]

Subjects will have no additional costs for participating in the study. Subjects, or their 3rd party payer, will be responsible for all standard-of-care charges including the blood transfusions that are routinely given to trauma patients. Subjects will not be charged for lab tests specifically performed for research purposes.

12.4 Protection Against Risks

12.4.1 Protection of Human Subjects and Consent

This trial qualifies for the "Exception from informed consent required for emergency research" outlined in the FDA regulation 21CFR50.24 as follows:

1. Subjects are in a life-threatening situation and collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular interventions
2. Obtaining informed consent is not feasible because the subject cannot give reasonable consent due to medical condition, intervention must be given before consent can be obtained from a LAR, and cannot prospectively select subject
3. There is prospect of direct benefit to subject because they are in a life-threatening situation requiring intervention, risks associated with this study are reasonable compared to standard of care therapy
4. The research could not practically be carried out without a waiver
5. Diligent attempts will be made to contact the LAR or family member for them to object to subject's continued study participation within the protocol-defined therapeutic window of the first 20 minutes and for the 24-hour study treatment duration

6. IRB has reviewed and approved the informed consent procedures and documents to be used with the subjects or LAR for this study.
7. Additional protection of rights will be provided which will include: community consultation and public notification, an established independent data safety monitoring committee, and efforts will be made to obtain informed consent from family members if the LAR is not available.

A detailed explanation of each criterion stipulated in the regulations for this exception and how our trial design applies to these criteria is outlined in Appendix 1. Once the subject is randomized, the site principal investigator or a designated member of the research team will make frequent attempts as soon as feasible, per local IRB/REB requirements, to contact a LAR and/or family member to provide information about the study and allow them the opportunity to withdraw the subject from continued participation in the study. A verbal withdrawal of the subject's further participation in the study will be considered binding. A log will be kept to document the attempts made to contact the LAR/family member. The log will be included in the paper data collection forms. Due to the severity of the injuries incurred, it is difficult to specify the time frame involved with obtaining the consent however all attempts will be made to obtain consent prior to completion of the study requested blood tests (72 hours after randomization). Attempts will continue to obtain consent from the LAR and/or patient throughout the hospitalization. Attempts to contact will include direct contact, telephone contact and written contact or any other contact options as approved by local IRB/REB policy. An assessment will be done at the time of approaching the LAR/subject for consent to assure the LAR and/or subject is competent to make a sound decision regarding the consent process. In the event that the subject does not survive following the traumatic injury, their information will be included in the data analysis. Written notification may be sent to the deceased's family regarding their participation in the study, per local IRB/REB policy.

Public notification and community consultation in accordance with local IRB and Canadian REB policies will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions, it will not be possible to target specific individuals although the local IRB/REB may recommend targeting specific groups. The community consultation plan for each trial site will be individualized to fit the IRB/REB requirements. The participating sites have considerable experience conducing community consultation. A variety of methods are employed including consultation with community leaders and targeted community groups, random telephone surveys,[105] and community meetings. Most sites provide an "opt out" process to individuals who do not want to be enrolled. The "opt out" process allows all members of the community to identify themselves if they choose to not be involved with the study. For this study, the "opt out" identifier (i.e., colored bracelet or identification card) will be determined by the local IRB/REB and will be made available through the community consultation programs. The identifier can be given to the individuals at time of meeting or mailed out to the individuals requesting the "opt out" process. Clinical research personnel will be trained to check for these patients prior to randomization.

A modified consent process will be conducted in the group of subjects who are screened, have initial blood drawn, and determined to be eligible (at the 0 hour blood draw) but are not randomized. The method of consent (i.e. waiver of consent, waiver of documentation, or full consent) will be dependent on the individual site's local IRB/REB policies and regulations.

The subject will be given the opportunity to continue or withdraw from the study when they become capable of providing informed consent. After all questions/concerns have been addressed, the subject will be given a consent form to sign, indicating whether he/she wants to continue or stop participating in the study. For those subjects considered as a minor, the one page consent form will be considered the assent form. If a LAR/family member previously signed the "Research Study Information and Consent Form," a copy of the signed form will be given to the subject.

12.4.2 Vulnerable Populations

While the NIH considers anyone under the age of 21 to be a part of the pediatric research group, there is wide variability in state laws defining the *adult* population. Taking this wide variability into consideration, all consent

related procedures, forms, and notification documents will be approved by the participating site's local IRBs or Canadian Research Ethics Boards (REBs) prior to the onset of the trial.

This trial may include subjects age 15 to 20. Subjects sixteen years of age and older are considered as adult trauma subjects in a large percent of the trauma centers. Sixteen and seventeen year olds are able to drive in most states and are at high risk for motor vehicle accidents resulting in blunt or penetrating injuries. Excluding this age group would significantly decrease our efforts to randomize 680 MT subjects in a two year period of time. Additionally, it is difficult to differentiate a 16 or 17 year old from one who is 21 or older at the time care is initiated in the ED until positive identification can be obtained. Children below the age of 15 or 50kg body weight will be excluded from this trial. Children's intravascular volume is different than the adult's, requiring adjustments to the standard adult treatment protocols. In addition, this trial will be conducted at Level I trauma centers which may or may not have affiliated pediatric programs.

Pregnant women will also be excluded from the PROPPR trial. Pregnant women have a significantly increased intravascular volume and physiologic reserve for bleeding which can require adjustments to the standard treatment protocols.

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

12.5 Roles/Responsibilities of Medical Monitor

An independent medical monitor will review all unexpected problems involving risk to subjects or others, SAEs and all transfusion-related deaths and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a SAE or transfusion-related death, comment on the relationship to participation in the trial. Because a large number of deaths are expected (30-70% mortality)[39] due to the condition of the study population at entry to the trial, individual reports to the DSMB will be aggregated and reported on a timely schedule acceptable to the DSMB. If the death is considered unexpected and is either suspected or probably due to treatment, this event would be promptly reported to the medical monitor and the DSMB. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for serious adverse events determined by either the investigator or medical monitor to be possibly or definitely related to participation must be promptly reported per FDA and/or Health Canada guidelines as described in Section 12.8.

12.6 Data Safety Monitoring Board (DSMB)

An independent DSMB has been established by the NHLBI. This committee will review and approve the protocol, and will develop a final plan for monitoring in collaboration with the HCCC, HDCC, ROC Management Committee and Trauma Committees, and NHLBI. The DSMB is governed by a charter that is designed for all ROC protocols.

The DSMB will help ensure the safety of the trial by monitoring adverse outcomes throughout the trial and by reviewing outcome data for possible harm. The DSMB will pay particular attention to missing 30-day mortality data. If the amount of missing 30-day mortality data approaches 10%, the DSMB will be asked to recommend specific changes to be made to the protocol in an effort to keep the value less than 10%. The committee reviews and approves the protocol and any amendments. In addition, the committee will review the results of the interim analyses. Although the DSMB and NHLBI will make the final decision about the interim monitoring plan, we anticipate that the DSMB will evaluate safety at intervals to be determined by the DSMB, expected to be approximately semi-annually but could occur more frequently if mandated by the DSMB. The DSMB will advise the investigators if a change in the protocol is warranted based on this interim monitoring. The DSMB will meet in person or by phone every six months or more often as decided by the DSMB.

12.7 Adverse Events

Expected Adverse Events

Common expected AE's/SAE's will include: trauma injury related infections, ventilator associated pneumonia (VAP), thrombotic complications (DVT, PE, MI, stoke), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), MOF and intracranial operative interventions.

Adverse Events Reporting Procedure

All adverse events will be classified by: a) Severity (AE, SAE); b) Expected vs. Unexpected; and c) Related vs. Unrelated. Unrelated adverse events, not of study interest will not be recorded on the subject's Adverse Events Log or entered into the eCRF. Only study-related adverse events or events that are outcome measures of interest that occur during the study period (after randomization until study conclusion) will be recorded.

12.8 Serious Adverse Events

Expected Serious Adverse Events

The study population is expected to have a large number of unrelated, expected serious adverse events including death from trauma related injuries. The SAE will be recorded on the subject's AE/SAE log and follow local reporting requirements.

Unexpected, Serious Adverse Events:

Serious Adverse Events will include potential transfusion-related events such as possible transfusion-related death and/ or transfusion-related acute lung injury (TRALI), re-hospitalizations, or other unexpected SAEs. The site PI will classify the relatedness of the SAE to the study intervention.

Serious Adverse Events Reporting Procedure

SAE reporting for the PROPPR study will follow the FDA guidance on safety reporting requirements for IND and BA/BE studies dated September, 2010. In addition to following local reporting procedures, clinical sites will notify the HCCC/HDCC of a SAE or suspected transfusion-related death within three business days of discovery of the event and complete a MedWatch 3500 form and/or Health Canada's ADR form. The HDCC will report transfusion-related deaths to the DSMB, FDA, Health Canada, NHLBI, and IRBs/REBs within seven calendar days of receiving the site report. All other unexpected and possibly related SAE's will be reported within 15 calendar days of receiving the site report.

Adjudication Procedures for Cause of Death Classification:

An adjudication process will be incorporated to determine the cause of death for the subjects enrolled in PROPPR.

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APPENDIX 1

Exception from Consent for Emergency Research

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

CFR Sec. 50.24 Exception from informed consent requirements for emergency research

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 investigations, is necessary to determine the safety and effectiveness of particular interventions.

The proposed study is a randomized trial of ratios of blood products (plasma:platelets:RBCs) in trauma patients who present with massive bleeding requiring transfusion within hours of injury. These patients are in an immediate life threatening situation. Although only 3% of admissions to civilian trauma centers and 7-10% of combat support hospital admissions require MT (defined as ≥ 10units of RBC's within 24hours of admission) , the majority of those patients receive MT in the first 3-6 hours after injury and have the highest incidence of death during that same time frame. Almost half of those civilian admissions suffer from truncal hemorrhage which is the leading cause of potentially preventable death with most deaths occurring within 6-12 hours of admission. In the combat support hospitals more than ¾ of all potentially preventable deaths are from truncal hemorrhage. Coagulopathy likely plays a significant role in preventable deaths due to hemorrhage as seriously injured patients in shock are the ones who most often present with coagulopathy in the ED. Trauma patients who are not coagulopathic rarely die. Trauma induced coagulopathy (TIC) is associated with *higher* transfusion requirements, a *greater* incidence of MOF, *longer* ICU and hospital stays, and a 4x risk of mortality compared to those with normal coagulation. Lack of a mechanistic understanding has led to wide variability in transfusion practice in seriously injured patients with wide variability in survival.

The deleterious impact of dilution-related abnormalities on coagulation and the impact of hypothermia, coagulopathy, and acidosis on survival have long been recognized. Although significant attention has been focused on preventing hypothermia and acidosis, little attention has been directed towards understanding the mechanisms involved with the early presentation of TIC. Indeed there is to date, no comprehensive and longitudinal characterization of the coagulopathic milieu after severe injury. Currently knowledge of the patterns of traumatic coagulopathy is extremely limited, and clinically useful diagnostic tools are essentially absent. Thus, therapeutic options are severely restricted

This proposed trial and these laboratory studies will define the understanding of the mechanisms of early coagulopathy associated with trauma, how best to mitigate and reverse the effects, and start describing optimal treatment regimens.

2. Obtaining informed consent is not feasible because:

- **i. The subject 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 (LAR) is feasible; and**
- **iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical intervention**

In order to perform this trial, the randomized intervention will be performed in the initial resuscitation period following patient arrival to the ED. As a result of the injuries, the patient is unable to provide consent for study enrollment. The patient will often be intubated and have altered mental status as a result of the injury. The legal next-of-kin are often not immediately available when the patient arrives to the ED. Because this trial involves

traumatic injury which is unpredictable, there is no way to prospectively identify individuals who are likely to become eligible for this trial. We will inform the family member or LAR at the earliest feasible opportunity of the subject's inclusion in the clinical investigation, the details of the investigation, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. Such notification is not usually feasible before or at the actual time of treatment and may be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible (unless otherwise directed by an IRB).

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.**
    - a. Subjects who are eligible for this trial are facing a life-threatening situation which will necessitate intervention including multiple units of blood products. There is currently no single standard of care for the ratio of blood products to be chosen and conflicting information from published research.
    - b. Previous observational studies have been done to evaluate the impact of product ratios associated with clinical outcomes
    - c. The subjects eligible for this trial have been determined to need a MT therefore the risks associated with this trial are risks associated with transfusion of blood products.

Risk/Benefit Assessment:

Eligible subjects for this trial will have been identified as requiring multiple units of blood products due to their traumatic injury. The risks associate with transfusion of any blood products include the chance of transmission of viral diseases, hypotension, allergic reactions, shortness of breath, blood clotting complications, hypoventilation and fever. These risk factors are minimized through the local blood center's protocols for infectious disease testing. Severely injured subjects who receive blood products will frequently incur complications such as death, multi-organ failure (MOF), respiratory complications, and infections. While there is no expectation of harm between groups, the risk of transfusion-related acute lung injury (TRALI) is increased as plasma and platelets use increases, however, most authors place this as a 1:10,000 rate, and this rate must be placed in the context of significantly decreased mortality reported in many recent publications.[25, 66]

There is a potential risk that products may be delayed due to the randomization process, however all participating sites will have plasma and RBCs rapidly available in the ED for use until the container with the randomized products is available. To monitor the potential risk, the clinical research staff will document relevant times including: time of ED admission, time of randomization, time MT called to the blood bank, and time study container delivered to bedside from the blood bank. If a delay or risk is identified, appropriate information/data will be sent to the DSMB to decide if further action needs to be taken.

This trial intends to benefit all subjects with the use of the MT algorithm to predict which subjects will require a massive transfusion. With the utilization of the algorithm we hope to predict earlier who will need blood products as well as those who will not require blood products. Other possible benefits for the treatment groups include decreased mortality, multi-organ failure, hospital length of stay and need for blood products. Additional benefits for the general population include 1) updated data regarding coagulopathy complications in trauma subjects and potential treatment regimens, and 2) the availability of a more precise algorithm to assist the trauma surgeons and emergency medicine physicians to predict the need for blood product transfusions.

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

This trial could not be conducted without the waiver of consent, due to the need to administer blood products rapidly upon recognition that a patient requires a MT.

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 LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact LAR and make this information available to the IRB at the time of continuing review.

The initial resuscitation time period for this trial begins at the time the patient arrives in the ED. MT protocols are often initiated within the first 10 minutes of ED arrival. Due to the nature of the injury and the intensity of the resuscitation efforts, it is not often feasible to obtain consent prior to the MT protocol being initiated and prior to randomization into the study. The legal next of kin are often not immediately available when the patient arrives to the ED. We will, however, make a reasonable attempt to contact a LAR for each subject at the earliest feasible opportunity to obtain consent rather than proceeding without consent. The LAR or family will be informed of the subject's inclusion in the clinical trial, the details of the trial, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefit to which the subject is otherwise entitled. Such notification is not usually feasible before or at the time of treatment and must be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible (unless otherwise directed by a local IRB/REB).

Where allowed or mandated by the local IRB/REB, a script will be available which can be used to inform patients or their LAR of the study and obtain verbal consent where feasible. In addition, due to the continuation of the intervention into the hospital, repeated attempts will be made to contact that patient or LAR at the earliest feasible opportunity after hospital arrival to notify them of study participation and seek consent for ongoing participation. Efforts to contact LARs will be tracked and reported to the local IRB/REB. Attempts will continue to obtain consent from the LAR and/or patient throughout the hospitalization. Attempts to contact will include direct contact, telephone contact and written contact of any other contact options as approved by local IRB/REB policy. An assessment will be done at the time of approaching the LAR/subject for consent to assure the LAR and/or subject is competent to make a sound decision regarding the consent process.

When approached for notification of study participation following enrollment, the patient or their LAR will have the option of withdrawing from the study. During the notification process, the details of the trial will be reviewed along with potential risks and benefits, the endpoints of interest and the process by which these endpoints are evaluated. When notified of trial enrollment, the patient or their legal representative will be given the opportunity to withdraw from further data and sample collection. If the patient or LAR withdraws, all further data collection and blood sampling will cease. A verbal withdrawal of the subject's further participation in the study will be considered binding. Data collected prior to the point of withdrawal or until subject is discharged from the hosptial will be reviewed for study purposes. All research laboratory samples collected up to the point of withdrawal will be obtained and analyzed. In this circumstance, we will be limited to a description of baseline data and data collected up to the point of patient withdrawal and survival to hospital discharge to ensure that subjects who withdraw are comparable among the groups. Our previous experience suggests that refusals of this nature are rare. It will be up to local IRBs/REBs to determine if and when a written consent form is required for continued participation.

As this is an emergency research study we will be seeking an emergency waiver of consent. We will contact the LAR for continued trial participation, at the earliest feasible time for the LAR to provide informed consent. All

study procedures already performed and yet to be completed will be explained, and the legal representative's consent for continued participation will be requested. If the subject becomes competent to provide consent during their admission, he/she will be approached by the research coordinator for approval for all study procedures including the 30-day follow-up interviews.

Taken together with the lack of current satisfactory treatment, the life-threatening nature of these trauma types, and the prospect of benefit to participants, these factors provide sufficient support for an emergency exception from informed consent in order to evaluate an intervention that may have significant outcome benefits to this patient population.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with FDA and HHS regulations. These procedures and the informed consent document are to be used with subjects or their LAR 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, consent forms and notification documents will be approved by the participating site's local IRBs or Canadian Research Ethics Boards (REBs) 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;

Public notification and community consultation in accordance with local IRB and Canadian REB policies will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions, it will not be possible to target specific individuals although the local IRB/REB may recommend targeting specific groups. The community consultation plan for each trial site will be individualized to fit the local IRB/REB requirements. The participating sites have considerable experience conducing community consultation. A variety of methods are employed including consultation with community leaders and targeted community groups, random telephone surveys,[105] and community meetings. Most sites provide an "opt out" process to individuals who do not want to be enrolled. The "opt out" process allows all members of the community to identify themselves if they choose to not be involved with the study. For this study, the "opt out" identifier (i.e., colored bracelet or identification card) will be determined by the local IRB and will be made available through the community consultation programs. The identifier can be given to the individuals at time of meeting or mailed out to the individuals requesting the "opt out" process. Clinical research personnel will be trained to check for these patients prior to randomization. Clinical research personnel will be trained to check for these patients prior to randomization.

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;

Our suggested approach to public disclosure/community consultation will follow techniques previously approved by local IRBs and employed at individual centers, such as random-digit dialing, open-forums, public announcements via newspaper or radio, and other locally approved methods of contact with the public. Visual aides, such as power point, flyers or posters can be used in the presentations, and all material will be in lay terminology. Each communication will include information as to the purpose of the trial, the consent process, the risk and benefits to the community/patient, and the time commitment required. As each community is unique and may require specific or special needs, the local IRBs/REBs will approve the methods for their community and ensure that community consultation practices are both appropriate and complete before consent is given to begin the trial.

During the course of public notification/community consultation, including public advertising of the study, individuals in the community not wishing to be enrolled in the trial will be provided opportunity to "opt out" in advance for treatment. Those contacting a published address and /or telephone number for the investigators will be given a bracelet or its equivalent without cost which, when displayed, indicates ineligibility for the study. A letter will accompany the bracelet/item indicating that it must be displayed on person in a recognizable manner in order to be identified by providers. Providers will be trained to recognize such bracelets or their equivalent, and that the identification of such an item would exclude the patient from trial enrollment.

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;

Public disclosures will be performed both prior to trial enrollment (with opportunity and a mechanism for the community to contact the investigators with their response) and at the completion of the trial in the form of multimedia press releases organized by the ROC and by local sites at the direction of the IRB/REB. These will include plans for the trial, including potential risks and benefits, and a summary of the results of the trial upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the trial. Information regarding the trial will also be available on the ROC website.

iv. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;

An independent data and safety monitoring committee will oversee the trial. Please see section 12.5 of the Protocol.

v. If obtaining informed consent is not feasible and a LAR 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 LAR, 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.

We expect that the majority of subjects who meet the enrollment criteria will either be unconscious or have an altered mental status secondary to acute blood loss, traumatic brain injury or intoxicating substances, and thus will not be in a position to provide informed consent in the ED setting. Accordingly, it may not be feasible to attempt to obtain informed consent during the therapeutic window. We will inform the family member or LAR at the earliest feasible opportunity of the subject's inclusion in the clinical trial, the details of the trial, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (See more details in item 5 above.) Such notification is not usually feasible before or at the actual time of treatment and must be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible (unless otherwise directed by a local IRB). A log will be kept to document the attempts made to contact the LAR/family member. The log will be included in the paper data collection forms.

APPENDIX 2

DATA COLLECTION FLOWSHEET

ASSESSMENTS	Pre ED	ED	OR	IR	Inpatient 1st 24 hrs	Inpatient Daily Assess.	Discharge Info	30 Days
Eligibility Criteria	x	x						
Demographics		x					x	
Trauma Activation	x							
EMS Care	x							
Unit arrival information		x	x	x	x			
Informed consent process		x	x	x	x	x		
Vital Signs	x	x	x	x	x	x		
Glasgow Coma Scale	x	x	x	x	x	x	x	
Extended Glasgow Outcome Score							x	
Mortality		x	x	x	x	x	x	x
Life Saving Interventions	x	x	x	x	x	x		
Injury Information	x	x						
Blood Products (including age of product)	x	x	x	x	x	x		
Non-blood Fluids	x	x	x	x	x	x		
Medications	x	x	x	x	x	x		
Surgical Procedures			x		x	x		
Interventional Radiology Procedures				x		x		
Angiogram				x				
Lab Results		x	x	x	x	x		
Hemostasis Obtained		x	x	x	x			
*Research Lab Sample Collection		x	x	x	x	x		
Multi-Organ Failure Assessment						x		
Complications					x	x	x	
Injury Severity Score (ISS)							x	
Subject Disposition							x	
Past Medical History							x	

* Research lab samples time points:
For all subjects (screened, eligible, or randomized): 0 hour
For all randomized subjects: 2, 4, 6, 12, 24, 48, and 72 hours

Care Guidelines

Summary of Care Guidelines, March 7, 2006

Preface: The trauma group has recognized and discussed the limitations of implementing care guidelines. The original recommendation for the use of the Glue Grant Guidelines has been relaxed to allow for the use of existing care guidelines that have the same intent, if not the same exact management. Where no pre-existing guidelines exist in an institution it is still expected that the Glue Grant Guidelines will serve as examples of good clinical practice and will be encouraged at ROC hospitals.

1.) Trauma resuscitation protocol: Tiered resuscitation efforts should include ATLS protocols and guide use of crystalloid administration and blood transfusion. Volume repletion efforts and restoration of hemodynamic stability may be guided by the use of CVP and/or PA catheters. The ultimate goal of resuscitation is restoration of oxygen delivery.

> Monitored in CRF on the Care Guideline Form: Assessment of the presence of either CVP or PA catheters in the first 48 hours of hospitalization.
> *Data is also collected regarding fluid totals every 12 hours for the first 24 hours after enrollment, including RBC use; 1st/worst ABGs, 1st/worst base deficit; 1st Lactate, 1st HGB and 1st coags are also monitored during the first four hours following ED admit.*

2.) Mechanical Ventilation Protocol: Goals include the use of a low tidal volume, lung-protective strategy is for patients meeting the criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) and the discontinuation of mechanical ventilation and/or extubation as early as possible based on frequent assessments of the patient's readiness to wean.

The widely accepted clinical criteria for ARDS is based on the American-European Consensus Conference on ARDS published in 1994.

Acute Lung Injury (ALI):

a) Hypoxia with a PaO_2/FiO_2 ratio >200, ≤ 300 *and*
b) Bilateral infiltrates on chest X-ray *and*
c) No clinical evidence of increased left atrial pressure or a pulmonary artery pressure of <18mmHg*

Acute Respiratory Distress Syndrome (ARDS):

a) Hypoxia with a PaO2/FiO2 ratio ≤200 *and*
b) Bilateral infiltrates on chest X-ray *and*
c) No clinical evidence of increased left atrial pressure or a pulmonary artery pressure of <18mmHg*

For those without pulmonary catheter, monitoring clinical evidence of left atrial hypertension includes:

- *a Acute myocardial infarction **or** known cardiomyopathy **or** severely reduced ejection fraction (<30%) **or** critical valvular disease*
- *b Chronic or acute oliguric renal failure with fluid input that exceeds output by ≥3 liters in the previous 24 hours.*

3.) Ventilator Associated Pneumonia, diagnosis and treatment: It is expected that each ICU will have a consistent definition of VAP. Various clinical criteria can be used to make the diagnosis, but utilizing quantitative lab values is encouraged when possible. Each ICU is expected to have guidelines regarding how to institute, contract and conclude antibiotic therapy.

4.) Guidelines for Glucose Control in the ICU: For critically ill patients with persistent blood glucose>110mg/dL, there should be standardized insulin infusion orders that target a defined level of glucose control.

5) Transfusion Guidelines: (Excluding of immediate resuscitation) it is recommended to limit transfusions for Hgb>7. NOTE: A higher transfusion trigger may be appropriate for patients with acute coronary syndrome and traumatic brain injury.

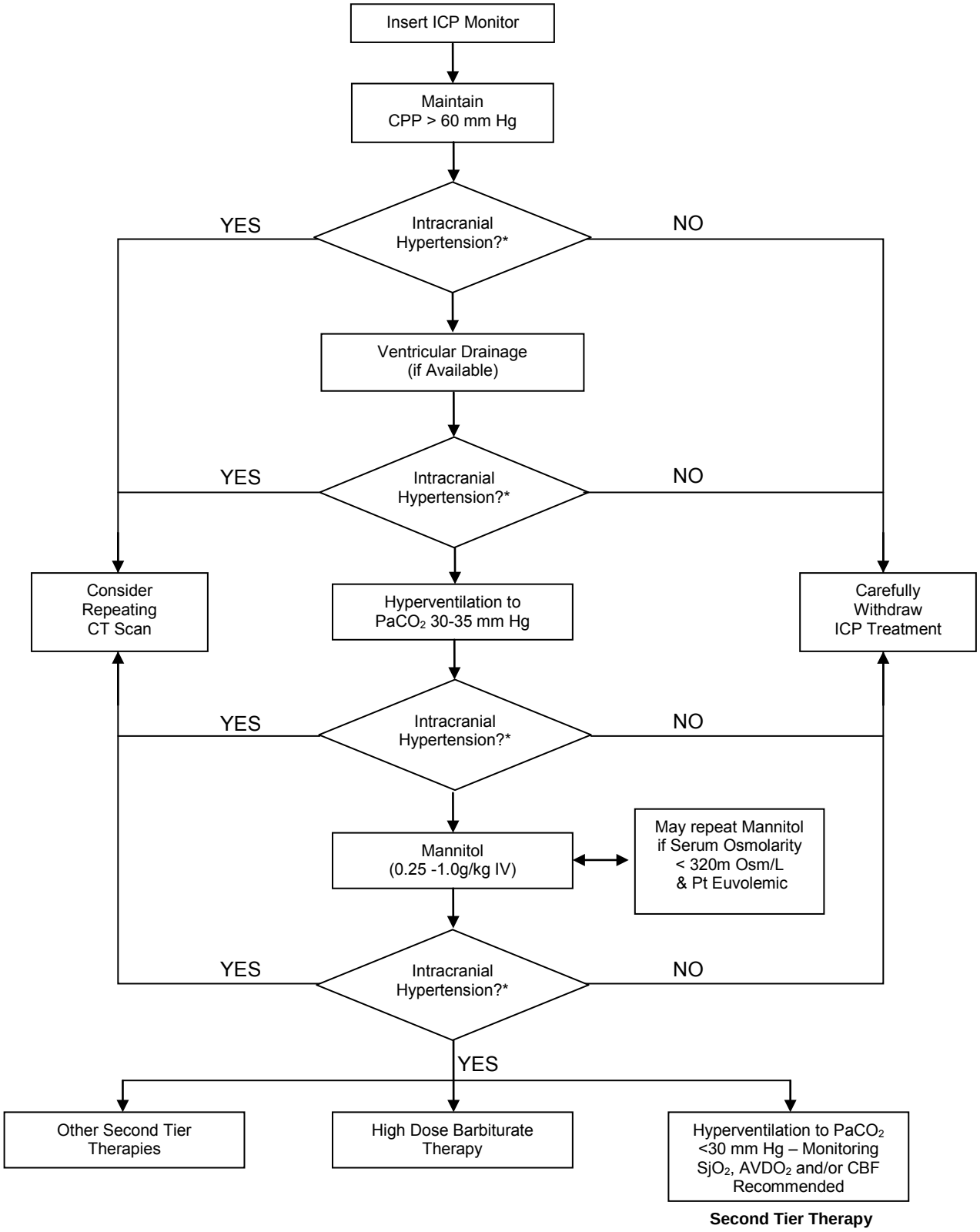
6.) Guidelines for sedation/analgesia of the mechanically ventilated patient. Recommend daily wake-up (sedation vacation) to limit ventilator day due to over sedation. An objective scoring instrument is also recommended to monitor sedation levels.

7.) Nutrition guidelines: Recommend early enteral nutrition to promote restoration of positive nitrogen balance.

8.) Management of Traumatic Brian Injury: (UNCHANGED)
All patients meeting the criteria for severe traumatic brain injury (persistent GCS<9) should have an intracranial pressure monitor placed. Patients with a sustained ICP>25mmHg should have intervention aimed at lowering ICP. This intervention is at the discretion of the treating physician but guided by the Brain Trauma Foundation Guidelines. Excess hyperventilation should be avoided unless the patient is showing signs of acute herniation. Patients should be resuscitated to avoid episodes of hypotension (SBP<90mmHg.)

There is also critical pathway for the treatment of established intra-cranial hypertension. It should be viewed as a framework that may be useful in guiding an approach to treating intra-cranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps. SEE NEXT PAGE:

Critical Pathway for the Treatment of Intracranial Hypertension



*Threshold of 20-25 mm Hg may be used. Other variable may bed substituted in individual conditions.

Critical Pathway for the Treatment of Established Intracranial Hypertension in the severe head injury patient. Adapted from the Brain Trauma Foundation, Inc.

Glue Grant Guidelines:

TR1: Clinical Protocol for Trauma Resuscitation

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Summary

The goal of this protocol is to guide consisted resuscitation efforts. Developed by expert consensus, this protocol progresses through a tiered approach to resuscitation, beginning with the widely accepted Advanced Trauma Life Support protocol. Since the majority of severe trauma patients present in shock due to excessive hemorrhaging, these patients require crystalloid administration and blood transfusion. The protocol aims for an optimal hematocrit of 30 during the acute resuscitation phase. If volume repletion efforts are inadequate to restore hemodynamic stability and hypovolemia is considered unlikely, a pulmonary artery catheter and/or echocardiogram may help rule out cardiac dysfunction as the etiology. Data from the pulmonary artery catheter are used to maintain an adequate, but not supranormal, cardiac index and oxygen delivery.

Protocol Goals

- Early recognition of the shock state for prompt initiation of resuscitation
- Ensure acute resuscitation of the trauma patient is conducted in a consistent manner
- Provide guidelines for the use of a pulmonary artery catheter (PAC) in the resuscitation of the major trauma patient.

Protocol Rationale

The primary objective of this protocol is to guide consistent resuscitation efforts for all eligible patients.[1,2] There is no level I research evidence on how to best resuscitate the severely injured trauma patient nor are there resuscitation parameters whose close monitoring (to guide intervention) clearly impact on patient outcome.[3-5] Further, the proof of benefit of a pulmonary artery catheter to guide resuscitation in a population of young, previously healthy subjects is limited.[3] Given the lack of available evidence, this protocol has been developed by expert consensus to promote a tiered approach to trauma resuscitation. The protocol begins with the widely accepted Advanced Trauma Life Support (ATLS) protocol and continues with the ATLS protocol until it becomes evident the patient is at high risk for post-traumatic organ failure, by virtue of an anticipated need for blood transfusion in the clinical context of either ongoing shock or evidence of impaired tissue perfusion (base deficit >6).[6]

Once a high-risk patient is identified, the patient should have a central venous pressure monitor placed in the subclavian or internal jugular position. If the central venous pressure (CVP) is high (CVP>15) an echocardiogram and early insertion of a pulmonary artery catheter should be considered to rule tamponade or cardiac dysfunction and to better guide resuscitation.

While the majority of severe trauma patients present in shock due to excessive hemorrhaging, the optimal hematocrit required to lower the risk of organ failure in patients with hemorrhagic shock is unknown, yet the risks of inadequate blood transfusion given the potential for ongoing blood loss are significant. As a result of compromise, the protocol aims for a minimum hematocrit of 30 during the acute resuscitation phase.

The protocol calls for volume repletion to a central venous pressure of 10-15 in the presence of sustained tachycardia and/or hypotension. If intravascular volume has been appropriately increased to this level and the patient remains unstable or has a persistent base deficit, there exists a component of cardiac dysfunction. At this point, a pulmonary artery catheter may be helpful to evaluate cardiac dysfunction.

Once data from the pulmonary artery catheter are available, the principal objective is to maintain an adequate (not supranormal) cardiac index (CI) if 3.8 l/min/m^2. There is little evidence to support supranormal resuscitation goals in this cohort of patients. Given a hemoglobin (Hgb) of 10g/dl and a reasonable oxygen saturation (SaO_2 > 90%), this should provide an oxygen delivery of over 450 ml/min/ m^2. Cardiac index is supported first through an increase in preload to a pulmonary capillary wedge pressure (PCWP) of at least 15, with an incremental increase to a PCWP no higher than 25 through repeated administration of intravascular volume boluses to achieve this endpoint (Starling curve). If there is no further increase in CI with repeated administration of fluid, then further administration of fluid to increase the PCWP is unwarranted. If the goal CI has not been attained, inotropic support should be strongly considered. In the presence of hypotension, consider the use of dopamine, norepinephrine, or epinephrine and continually re-assess for ongoing bleeding or hypovolemia. Without hypotension, dobutamine (or Milrinone) should be selected at the discretion of the attending physician.

Occasionally, there are circumstances where there is persistent hypotension despite an adequate cardiac output. Continued re-evaluation for bleeding and/or hypovolemia is indicated. Once addressed, an agent with vasopressin properties should be considered. The specific choice of agent (norepinephrine, vasopressin, or dopamine) is at the discretion of the attending physician.

Protocol details

1. Begin resuscitation using the standard ATLS protocol.
2. Identify the high risk patient:
    - Anticipated need for blood transfusion AND
    - Continued base deficit >6 OR systolic blood pressure <90 mm Hg

3. Insert central venous pressure monitor in the subclavian or internal jugular vein.
4. If sustained heart rate (HR) >120 or systolic blood pressure (SBP) <90, administer blood and crystalloid to Hgb of 10 and CVP of 15 until HR <120 or SBP >90.
5. If sustained HR> 120 or SBP <90 and CVP ≥15, consider cardiac dysfunction or tamponade and insert a pulmonary artery catheter (PAC) and consider pericardial ultrasound or echocardiogram.
6. Insert a PAC if there is no improvement in base deficit despite administration of blood and crystalloid to Hgb of 10 and CVP of 10-15.
7. Once a PAC is inserted, aim for CI 3.8
    - If CI <3.8 and PCWP <15, administer crystalloid to PCWP =15
    - If CI <3.8 and PCWP >15 and PCWP <25, administer 500cc crystalloid (or blood as appropriate) boluses with repeat measurement of CI and PCWP within 5 minutes after each bolus (Starling curve)
    - If CI drops by 0.3, record prior PCWP as “optimal” and maintain this PCWP with crystalloid (and/or blood to maintain HBG 10)
    - If CI <3.8 and optimal PDWP has been attained (or PCWP 25), begin inotrope of choice to achieve CI > 3.8; consider echocardiogram
    - If CI < 3.8 with MAP _60, re-evaluate for bleeding and/or hypovolemia, then treat with an inotrope with vasopressor effects (e.g. dopamine, levophed or epinephrine)
    - If CI _3.8 with MAP_60, then treat with a vasopressor (e.g. levophed or vasopressin)

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5. McKinley BA, Kumar RA, Coca our CS, Maldivian A, Sailors RM, Ware DN et al. Normal versus supranormal oxygen deliver goals in shock resuscitation: the response is the same. J Trauma. 2002; 53(5):825-832.
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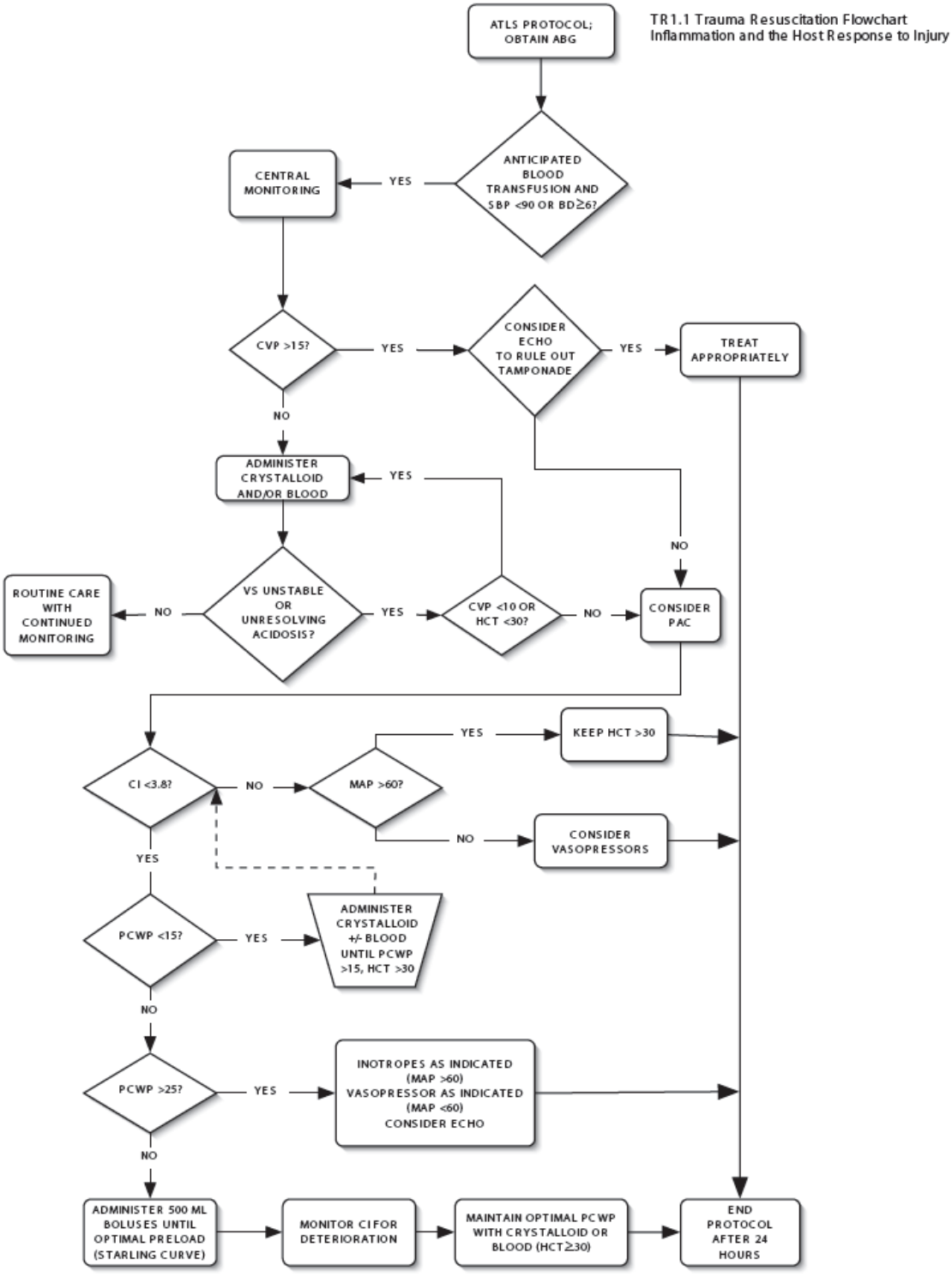
Accompanying Document

TR1.1 Trauma Resuscitation Flowchart

Published on www.gluegrant.org in May 2004 by the Inflammation and the Host response to Injury Investigators. Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.



TR2: Clinical Protocol for Mechanical Ventilation

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Summary

This protocol promotes a low tidal volume, lung-protective strategy for ventilating patients meeting the criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). To achieve adequate oxygenation, variable positive end-expiratory pressure (PEEP) and inspired oxygen (FiO2) is left to physician discretion, but the FiO2 to PEEP ratio should be less than or equal to 5. If arterial oxygenation is not within the target range, then either fiO2 or PEEP should be adjusted within 30 minutes, after which oxygenation should be reassessed within 15 minutes and subsequent adjustments made if necessary. The mode of mechanical ventilation is left to physician discretion; however, once patients are ready to wean, a daily trial of spontaneous breathing offers the best chances for early extubation. If the patient cannot be weaned from mechanical ventilation, the protocol recommends gradual reduction in breathing support, at the physician's discretion. In these patients, subsequent cycles of spontaneous breathing, weaning, and breathing support overnight for rest should be continued daily until the patient is breathing independently.

Protocol Goals

- Ensure that a low tidal volume, lung protective strategy is used for the ventilation of subjects who meet criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
- Provide guidelines for the use of PEEP inpatients with ALI or ARDS
- Ensure discontinuation of mechanical ventilation and/or extubation occur at the earliest possible time

Protocol Rationale

There exists Level 1 research evidence supporting a lung protective strategy using low-tidal volume (Vt) ventilation in patients meeting criteria for ALI or ARDS. Described in detail at http://hedwig.mgh.harvard.edu/ardsnet/studies.html , this strategy demonstrated a 23% reduction in mortality in patients treated with a protocol designed to limit alveolar stretch using a tidal volume of 6 mls/kg compared to subjects ventilated at a tidal volume of 12 mL/kg.[1]

It remains unknown if there exists any benefit to higher levels of PEEP compared with higher levels of FiO_2 in patients with ALI or ARDS. The only available Level 1 evidence

comparing higher levels of PEEP to higher inspired oxygen concentrations with lower levels of PEEP suggests there is no benefit to one strategy or the other. This randomized controlled trial was stopped due to lack of efficacy after enrollment of 550 patients and has not yet been published (http://hedwig.mgh.harvard.edu/ardsnet/ards04.html).

In patients without ALI or ARDS, no specific mode of mechanical ventilation is known to offer any advantage. As such, the decision about the mechanical ventilation mode is left to physician discretion. Once a patient is ready to wean, it appears that a daily trial of spontaneous ventilation offers the greatest potential for early extubation. This approach is superior to gradual withdrawal of ventilation using pressure support or intermittent mandatory ventilation. [2-5] In patients requiring prolonged ventilation, there is no conclusive evidence that airway management (intubation versus “early” tracheotomy) has an impact on outcome.

Protocol Summary

- Patients with ALI or ARDS as defined by a PaO_2/FiO_2 ≤300 and bilateral pulmonary infiltrates are managed by following a low tidal volume, lung protective mechanical ventilation strategy with the expectation this lung protective strategy is achieved (i.e. Vt ≤6 ml/kg) within 24 hours of meeting ALI criteria.
- Patients without ALI are managed by conventional mechanical ventilation. The specific mode of mechanical ventilation is left to physician discretion. Should ALI criteria be met subsequently, the patient is managed utilizing the low tidal volume strategy.
- Once the patient meets readiness to wean criteria, a daily trail of spontaneous breathing is performed. If this trail is successful, it is expected that the patient is extubated or otherwise liberated from mechanical ventilation.
- If readiness to wean criteria are met, but the patient is not likely to be successfully liberated from mechanical ventilation or does not demonstrate the ability to protect the airway, a procedure for gradual reduction in ventilatory support is instituted consistent with patient tolerance. The specific mode of weaning is left to physician discretion.
- All patients who meet readiness to wean criteria, but are not successfully liberated from mechanical ventilation after the weaning process receive sufficient mechanical ventilatory support overnight to rest and prevent occult fatigue.
- The cycle of spontaneous trial of breathing, weaning and rest are continued daily until the patient is liberated from mechanical ventilation.
- Airway management strategies (continued end tracheal intubation versus tracheotomy) are left to the treating physician’s discretion.

Protocol Details

Initial Ventilator Settings

- Tidal Volume (Vt)
- Vt calculations are based on predicted body weight (PBW) as follows:

- For males: PBW = 50 + 2.3 [height (inches) – 60]
- For females: PBW = 45.5 + 2.3 [height (inches) – 60]
- Initial Vt is set at 8mL/kg PBW. This setting is reduced by 1 mls/kg PBW at intervals of <2 hours until Vt = 6 mls/kg PBW.

Ventilator rate

- Initial ventilator rate is set at 12 -20 breaths per minute if possible. Maximum rate setting is 35 breaths/minute.

Subsequent Ventilator Adjustments

Ventilator rate and tidal volume are adjusted to achieve arterial pH and end-aspiratory plateau pressure goals, respectively.

Arterial pH

- The goal is to maintain the arterial pH between 7.25 and 7.45 Arterial pH is measured upon admission to the ICU and then every morning as well as 15 minutes after every change in tidal volume or respiratory rate. The clinical setting and physician discretion dictate additional measurement. Suggested management of alkaloid and acidemia is as follows;
- Alkaloid (pH >7.45) Decrease ventilator rate
- Mild acidemia (7.15 ≥pH <7.25) Increase ventilator rate up to maximum of 35 or until pH>7.25 or $PaCO_2$ <25mm Hg. If ventilator rate = 35 or $paCO_2$ <25, then bicarbonate infusion may be administered.
- Severe acidemia (pH <7.15) increase ventilator rate to 35. If ventilator rate = 35 and pH <7.15 and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until pH >7.15. Under these conditions, the target plateau pressure described below may be exceeded.

End-inspiratory plateau pressure goals: ≤ 30 cm H_20

- Plateau pressures are measured and recorded every eight hours and 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients must be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause is recorded. The pause is removed for at least 6 breaths, and repeated at least twice. The mean of at least 3 replicates represents the plateau pressure.
- If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressures are substituted.
- Tidal volumes are reduced by 1 ml/kg PBW q2 hours if necessary to maintain plateau pressures less than or equal to 30 cm H_20 (if arterial pH <7.15, tidal volume needs not be reduced; see “suggested management of severe academia”). Measure arterial pH 15 minutes following every change in tidal volume.
- The minimum tidal volume is 4 mL/kg PBW. If the tidal volume is less than 6 mL/kg and plateau pressure is <25 cm H_20 then Vt is increased in 1mL/kg PBW increments until plateau pressure is 25-30 cm H_20 or Vt = 6 mL/kg PBW.

Oxygenation

Target ranges for oxygenation are 55 mm Hg is less than or equal to PaO_2 is less than or equal to 80 mm Hg, or 88% is less than or equal to SpO_2 is less than or equal to 95%. When PaO_2 and SpO_2 measurements are available simultaneously, the PaO_2 measurement takes precedence. When oxygenation goals are achieved, the FiO_2 should be weaned down to <0.67 at the earliest possible time. The PEEP and theFiO_2 combinations used to achieve the goals above are left to physician discretion, but as a general rule the FiO2 (as a percentage) to PEEP ratio should be less or equal to 5.

When increasing PEEP above 10 cm H20, do so by 2-5 cm H_20 increments to a maximum of 35 cm H_20 or until PaO_2 = 55-80 mm Hg or SpO_2 = 88-95%. If the PEEP increase does not lead to an increase inPaO_2 of >5 mm Hg within 4 hours, PEEP is set to the last level that achieved a response.

Arterial oxygenation can be assessed by either SpO_2 or PaO_2 at a minimum of every 4 hours.

If arterial oxygenation is not within the target range, then either FiO_2 or PEEP should be adjusted within 30 minutes. Following adjustments, oxygenation is reassessed within 15 minutes and subsequent adjustments are made if necessary.

If PaO2 <55 mm Hg or SpO_2 <88% and tidal volume = 4mL/kg PBW (or the minimum tidal volume necessary for pH control) and plateau pressure > 30 cm H_20m then FiO_2 is raised until PaO_2 = 55-80 mm Hg or SpO_2 = 88-95% or FiO_2 = 1.0. If PaO_2 <55 mm Hg or SpO_2 <88% and FiO_2 = 1.0, PEEP is raised to achieve adequate oxygenation. In these circumstances, plateau pressure may exceed 30 cm H2O. Brief periods (5-10minutes) of SpO_2 <88% or >95% may be tolerated without making changes in PEEP or FiO_2. FiO_2 = 1.0 may be used for brief intervals (10 minutes) of transient desaturation or to prevent desaturation during treatments such as tracheo-bronchial suctioning or position changes.

Changes in more than one ventilator setting driven by measurement of PO_2, pH and plateau pressure may be performed simultaneously if necessary.

Assessment of readiness to wean

Patient assessment of the following criteria should be performed each day between the hours of 0400 and 0800. If the assessment is precluded by procedures or other extenuating circumstances, the assessment and initiation of weaning procedures may occur later in the day, but should not be held off to the next day.

A. Resolution or stabilization of the underlying disease process leading or contributing to the requirement for mechanical ventilation
B. Not receiving neuromuscular blocking agents and without residual effects of neuromuscular blockade
C. Exhibiting respiratory efforts

D. Hemodynamically stable with no inotropic or vasopressor support (less than or equal to 5µg/kg/min of dopamine or dobutamine will not exclude patients from consideration for liberation).
E. FiO2 less than or equal to 0.5 and PEEP less than or equal to 10 CM H_2O
F. PaO2 > 75mmHg
G. Ve<15L/min
H. Ve>80% of Ve mechanical
I. pH between 7.30 and 7.50

Trial of spontaneous breathing protocol

All patients receiving mechanical ventilation who are considered ready to wean are evaluated on a daily basis for the ability to tolerate unassisted ventilation by means of a 30-90 minute trial of spontaneous breathing between the hours of 0500 and 0900. If circumstances preclude the conduct of the trial at this time of the day, the assessment and trial can be performed later in the day, but should not necessarily be held off to the next day. A trial is attempted unless there is a physician order to delay the trial.

- A 30-90 minute trial of spontaneous breathing is performed with the continuous positive airway pressure (CPAP) setting set to the current PEEP setting, no greater than an inspiratory pressure support of 8 cm H_2O and FiO_2 equal to current FiO_2. (FiO_2 at the initiation of the trial may be increased by 0.1 above previous FiO_2 at the discretion of the physician.)
- If the patient meets any one of the criterion below, the trial is terminated and the patient is returned to the previous ventilator settings:
  Respiratory rate > 35 for ≥ 5 minutes
  SpO_2 <90% for ≥ 30 seconds
  Heart rate >140 beats/minute or sustained heart rate increase or decrease of 20% from baseline; systolic BP >180 mm Hg or <90 mm Hg
  Sustained increase in anxiety, diaphoresis, or other signs of respiratory distress
  Cardiac instability or dysrhythmias
  pH less than or equal to 7.32
- The patient should be evaluated for transient issues that may negatively influence a trial of spontaneous breathing (that is, excess sedation, agitation, acidemia, etc.). In theses cases, another assessment should be made later in the day when the issue has been resolved. Otherwise, the patient should be returned to the previous mechanical ventilator settings and weaning commenced as ordered by the attending physician.

Assessment of readiness for extubation

If the patient successfully completes a trial of spontaneous breathing, the following criteria should be assessed to determine readiness for extubation:

- Does not require suctioning more than every 4 hours
- Anticipated good spontaneous cough

- Endotracheal tube cuff leak with less than or equal to 30 cm H_2O positive pressure
- No known history of upper airway obstruction or stridor within the prior 48 hours
- No known history of reintubation for bronchial hygiene within the prior 48 hours

The therapist should notify the primary physician team of the protocol success and discuss readiness for extubation criteria. If the physician decides not to extubate, the patient may be placed on a T-piece, with CPAP equal to the PEEP setting on the ventilator or on a low level of pressure support (PS <8).

For the purposes of this protocol, all of the following are considered unassisted breathing

- Extubated with face mask, nasal prong oxygen, or room air OR
- T-tube breathing OR
- Tracheostomy mask breathing, OR
- CPAP=5 without PS (PS >8) or intermittent mandatory ventilation (IMV) assistance

If the patient fails the trial of spontaneous breathing, the patient may be weaned using a mode of ventilation prescribed by the treating physician. The patient must rest overnight and another assessment of readiness to wean and a trial of spontaneous breathing (if ready to wean) should be conducted the following morning.

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Accompanying documents

TR2.1 Mechanical Ventilation Protocol Pocket Card 3x5 Inch Side 1
TR2.1 Mechanical Ventilation Protocol Pocket Card 3x5 Inch Side 2

Published on www.gluegrant.org in May 2004 by the Inflammation and the Host response to Injury Investigators.
Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.

TR2.1 Mechanical Ventilation protocol 3x5 Inch Pocket Card
Inflammation and the Host Response to Injury
Patients with ALI Or established ARDS (PaO_2/FiO_2 ≤300, bilateral pulmonary infiltrates) aim for the following within 24 hrs of meeting criteria:

- Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 ml/kg at intervals of < 2 hours until the tidal volume = 6mL/kg. Tidal volume calculations are based on predicted body weight as follows:
  For males: PBW = 50 + 2.3 [height (inches) – 60]
  For females: PBW = 45.5 + 2.3 [height (inches) – 60]
- PaO_2 55088 mm Hg or PaO_2 88%-95%. FiO_2/PEEP ratio should be ≤5 and PEEP must be ≤ 35 cm H2O
  pH 7.25-7/45 with RR < 35 and $PaCO_2$ ≥ 24. HCO_3 infusion may be given if necessary. If pH<15 then Vt may be increased by 1 mL/kg to pH ≥7.15 and target plateau pressures (see below) may be exceeded
- Plateau pressures (PP) ≤ 30 cm H_2O. Reduce Vt to no less than 4 mL/kg. If Vt <6 mL/kg and PP < 25 then increase Vt until PP = 25-30 of Vt + 6 mL/kg

Patients not meeting ALI/ARDS criteria can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

Patients should undergo a daily assessment of readiness to wean: (a) resolution or stabilization of the underlying disease process; (b) no residual effects of neuromuscular blockade; (c) exhibiting respiratory efforts; (d) hemodynamically stable; (e) FiO_2 ≤ 0.5 and Peep ≤8 cm H_2O; (f) PaO_2 >75 mm Hg; (g) Ve <15 L/min; (h) Ve spontaneous ≥ 80% of Ve mechanical; (i) pH between 7.30 -7.50. If not ready to wean, then return to previous mode of ventilator support and reassess daily.

If ready to wean, then the patient should receive **a trial of spontaneous breathing (SBT) for 30-90 minutes:** otherwise continue weaning using a mode of ventilation selected at the discretion of the treating physician.

Criteria for **failure of a SBT**: (a) RR > 35 for ≥ 5 minutes; (b) SpO_2 <90% for ≥ 30 seconds; (c) HR >140 or increase or decrease of 20% from baseline; (d) SBP >180 mm Hg or <90 mm Hg; (e) Sustained evidence of respiratory distress; (f) cardiac instability or dysrhythmias; (g) pH ≤7.32. If any criteria are met, the CPAP trail is terminated and patient returned to previous ventilator settings and rested overnight. Repeat CPAP trial in the morning.

If patient completes a CPAP trial, the following criteria should be assessed to determine **readiness for extubation** and patient extubated if possible: (a) Does not require suctioning more than Q4 hours; (b) good spontaneous cough; (c) endotracheal tube cuff leak; (d) no recent upper airway obstruction or stridor; (e) no recent reintubation for bronchial hygiene.

TR3: Clinical Protocol for the Prevention, Diagnosis and Treatment of Ventilator-Associated Pneumonia

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Summary

This protocol addresses ventilator-associated pneumonia (VAP). Prevention of VAP is best accomplished through adequate hand washing, inclining the patient 30 degrees or more, avoiding gastric over distention, and maintaining the patient's oral hygiene. Various clinical criteria can be used to diagnose VAP. Patients with a threshold clinical pulmonary infection score (CPIS) greater than 6 should be evaluated for pneumonia. Quantitative protected sampling of the lower respiratory tract can help distinguish between colonization and infection. In contrast, quantitative Endotracheal aspiration cannot be considered sensitive or specific enough to accurately diagnose VAP. Quantitative protected-specimen brush obtained via bronchoscopy may be useful, but both the sensitivity and specificity of this analysis varies considerably among patients. It is critical that treatment of suspected VAP should begin with early, empiric therapy titrated to common organisms, as defined by the local anitbiogram for the unit in question. Inadequate antibiotic coverage significantly increases mortality in these patients. On the other hand, if no sign of infection is found, antibiotic therapy should be halted so as to prevent superinfection and secondary pneumonia from resistant organisms.

Protocol Goals

- Describe techniques utilized to minimize the incidence or VAP
- Define the minimal criteria to meet the diagnosis of VAP
- Describe the general regimens used in the treatment of VAP

Protocol Rationale

This protocol is based on available published literature recognizing the criteria that define VAP are not clearly standardized. It should be recognized that even when there are "good" data to support guidelines for the management of VAP, the patient populations studied in the literature were seldom severely injured patients for the most part.

Prevention of VAP

The following recommendations, published by the Centers for Disease Control and Prevention (CDC) and available at http://www.cdc.gov/, are supported by at least one randomized, controlled trial.

- Adequate hand washing between patients.
- Semi-recumbent positioning of the patient to > 30 degrees.

- Avoidance of gastric over-distention.
- Routine oral hygiene as part of daily care.

Diagnosis of VAP

There is no “gold standard” criteria that define VAP. Initial calculation of a CPIS is used to screen patients for presumed VAP1. Use of this score allows comparison of patients treated for pneumonia across study sites. Patients with a CPIS of <6 have little chance of having pneumonia in a group of hospitalized medical patients. Patients with a CPIS>6 are evaluated for pneumonia. The rationale is that there is no microbiological diagnostic test that is 100% specific for VAP and use of this score threshold minimizes the risk that patients with few clinical signs and symptoms of VAP will have false-positive culture results with subsequent administration of antibiotics.[2]

Recent studies to evaluate criteria for treatment with antibiotics for a presumed diagnosis of VAP have utilized data from quantitative protected sampling of the lower respiratory tract. Quantitative cultures, while not 100% sensitive and specific, can help distinguish between colonization and infection. Identification of the most likely organism can lead to antibiotic de-escalation once sensitivities are known. These studies suggest that clinical management strategies based on an invasive diagnostic procedure (bronchoalveolar lavage (BAL) or protected specimen brush (PSB) leads to improved survival and decreased antibiotic complications compared with strategy based on clinical guidelines without protected lower respiratory tract sampling.[3]

There are a number of techniques that can be utilized for quantitative evaluation. Quantitative endotracheal aspiration cannot be considered sensitive or specific enough to accurately diagnose VAP. The sensitivity of quantitative BAL obtained via bronchoscopy ranges from 42 to 93% (mean, 73%) and the specificity ranges from 45 to 100% (mean, 82%). The sensitivity of quantitative PSB obtained via bronchoscopy ranges from 33 to 100% (mean 67%) and the specificity ranges from 50 t0 100% (mean, 95%). Finally, blinded specimen collection techniques demonstrated sensitivity that ranges from 60 to 100% and specificity that ranges from 70 to 100%.

The threshold values used for a positive quantitative culture are those values presently used by the CD and generally accepted in the medical literature (available at http://www.cdc.gov/ncidod/hip/nnis/members/members.htlm).

Treatment of VAP

Treatment of suspected VAP should begin early with empiric therapy directed at the typical antiobiogram for the given unit location. At least 4 studies have shown if the initial antibiotic therapy is inadequate to cover the organisms that are ultimately isolated, then mortality is significantly increased.[4] Further, if antibiotic selection is either withheld or escalated once the culture results are known, mortality is still greater than if the correct antibiotic selection had been made empirically at the start of treatment.

Discontinuation of antibiotics if BAL cultures are negative is supported in the literature. It has also been shown that unnecessary use of antibiotics for VAP increases the

likelihood of superinfection with multi-resistant organisms. Recent data suggest that antibiotics can be stopped once clinical signs of infections have resolved rather than fixed duration of antibiotic therapy. Discontinuation of antibiotics may also decrease the incidence of secondary pneumonias with multi-resistant organisms. [5]

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Unnumbered Reference

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ACCOMPANYING Document

Tr3.1 Ventilator-Associated Pneumonia Flowchart

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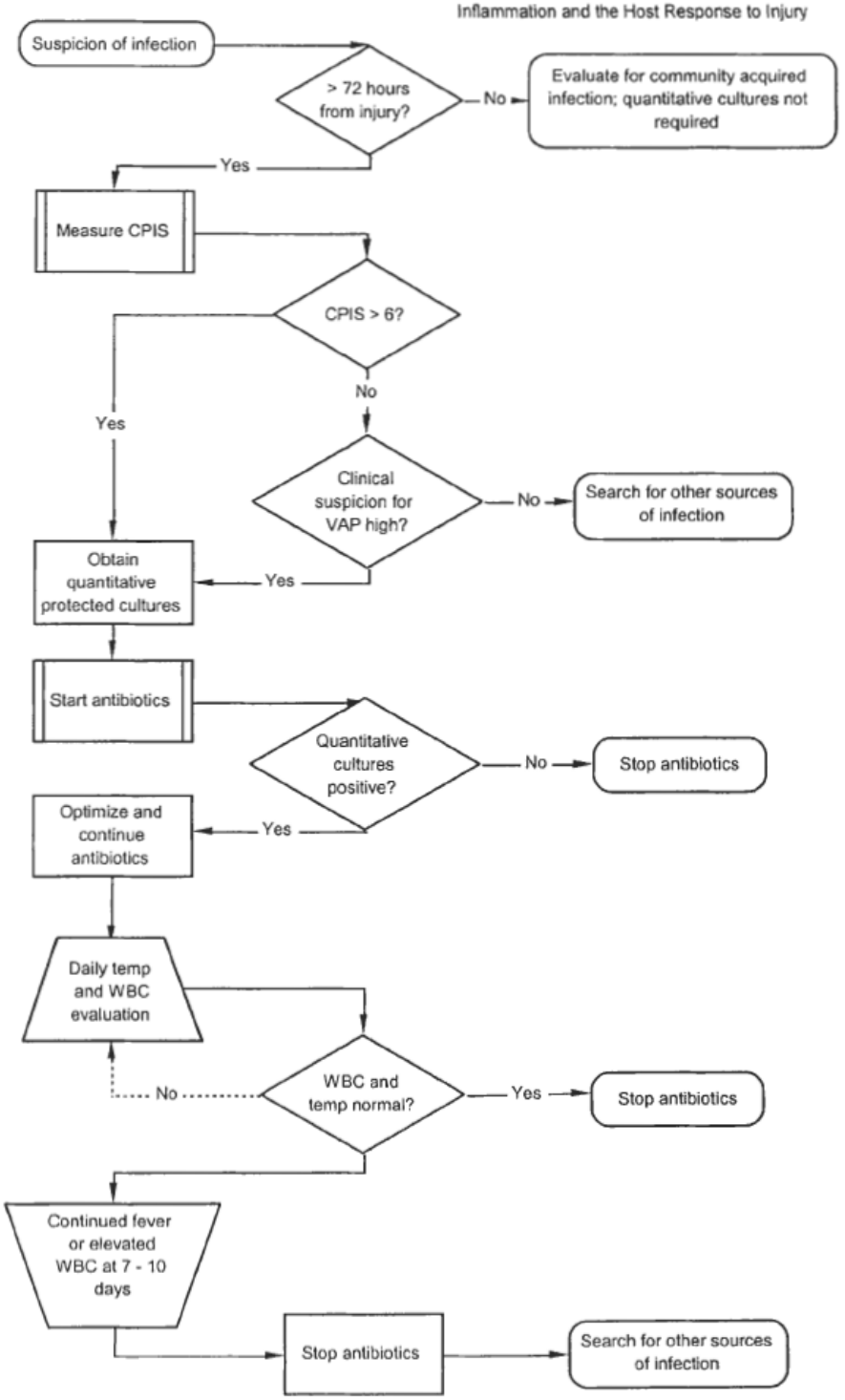
Supported by a large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.

TR3.1 Ventilator-Associated Pneumonia Flowchart
Inflammation and the Host Response to Injury



TR4: Insulin Infusion Orders

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Goal: Blood Glucose 80-110mg/dL

1. Indication : Critically ill patients with persistent blood glucose>110mg/dL
2. Monitoring:
   - Check blood glucose q 2 hrs and q 1 hr prn
   - If tube feed, TPN or fluids with D5W are stopped; decrease insulin infusion rate by 50 and check blood glucose q 1 r
   - **If blood glucose decreases by >50mg/dL and is still elevated** keep infusion at current rate and recheck blood glucose in 1 hour
   - Do NOT bolus for Serum Creatinine (SCr) >2

3. Initiation

Blood Glucose (mg/dL)	Bolus IV Push (units)	Infusion Rate (unit per hour)
111-150	2	1
151-200	2	2
201-250	4	2
251-300	6	4
301-350	8	4
>350	10	4

4. Continuation of insulin infusion:

Blood Glucose (mg/dL)	Bolus IV Push (units)	Infusion Rate (unit per hour)
< 60	0	d/c infusion; give ½ ampoule D50 IV push; recheck blood glucose in 30 minutes NAD if blood glucose >80 resume insulin infusion at 50 % of previous rate
60-79	0	d/c infusion; recheck blood glucose in 30 minutes AND if blood glucose >80, resume insulin infusion at 50% of previous rate
80-110	0	No change; if blood glucose continues to decrease within desired rage over 4 hour; decrease rate by 20%**
111-150	0	Increase rate by 20%**
151-200	2	Increase rate by 20%**
201-250	4	Increase rate by 20%**
251-300	6	Increase rate by 20%**
301-350	8	Increase rate by 20%**
>350	10	Increase rate by 20%**

** See below for rounded rate adjustment of 20 % (increase or decrease)

5. If infusion rate = 30 units /hour; notify H.O and continue to bolus per protocol as indicated by blood glucose. Do not increase infusion rate. Check blood glucose q 1 hr

** 20% adjustments (in u/hr)		
Current rate	Increase rate	Decrease rate
.05	1	0
1	1.5	0.5
1.5	2	1
2	2.5	1.5
2.5	3	2
3	3.5	2.5
3.5	4	3
4	4.5	3
4.5	5	3.5
5	5.5	1
5.5	6	1.5
6	6.5	2
6.5	7	2
7	8	2.5
7.5	8.5	6
8	9	6.5
8.5	10	7
9	11	7
9.5	1105	7.5
10	12	8
10.5	12.05	8.5
11	13	9
11.5	14	9
12	14.5	9.5
12.5	15	10
13	15.5	10.5
13.5	16	11
14	17	11
14.5	17.5	11.5
15	18	12

** 20% adjustments (in u/hr) *cont'd*		
Current rate	Increase rate	Decrease rate
15.5	18.5	12.5
16	19	13
16.5	20	13
17	20.5	13.5
17.5	21	14
18	21.5	14.5
18.5	22	15
19	23	15
19.5	23.5	15.5
20	24	16
21	25	17
21.5	26	17
22	26.5	17.5
22.5	27	18
23	27.5	18.5
23.5	28	19
24	29	19
24.5	30	19.5
25	30	20
25.5	30	20.5
26	30	21
26.5	30	21
27	30	21.5
27.5	30	22
28	30	22.5
28.5	30	23
29	30	23
29.8	30	23.5
30	30	24

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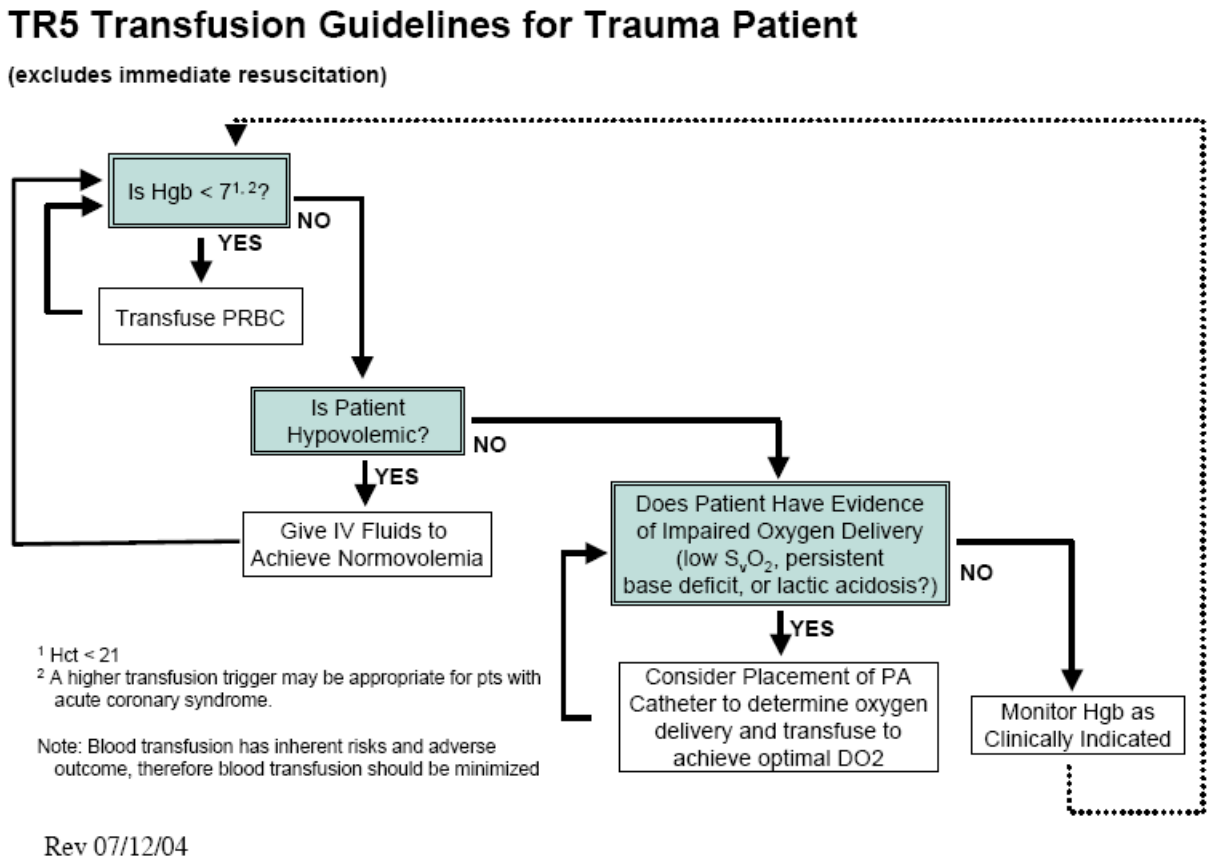
TR5: Transfusion Guidelines for Trauma Patient

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.



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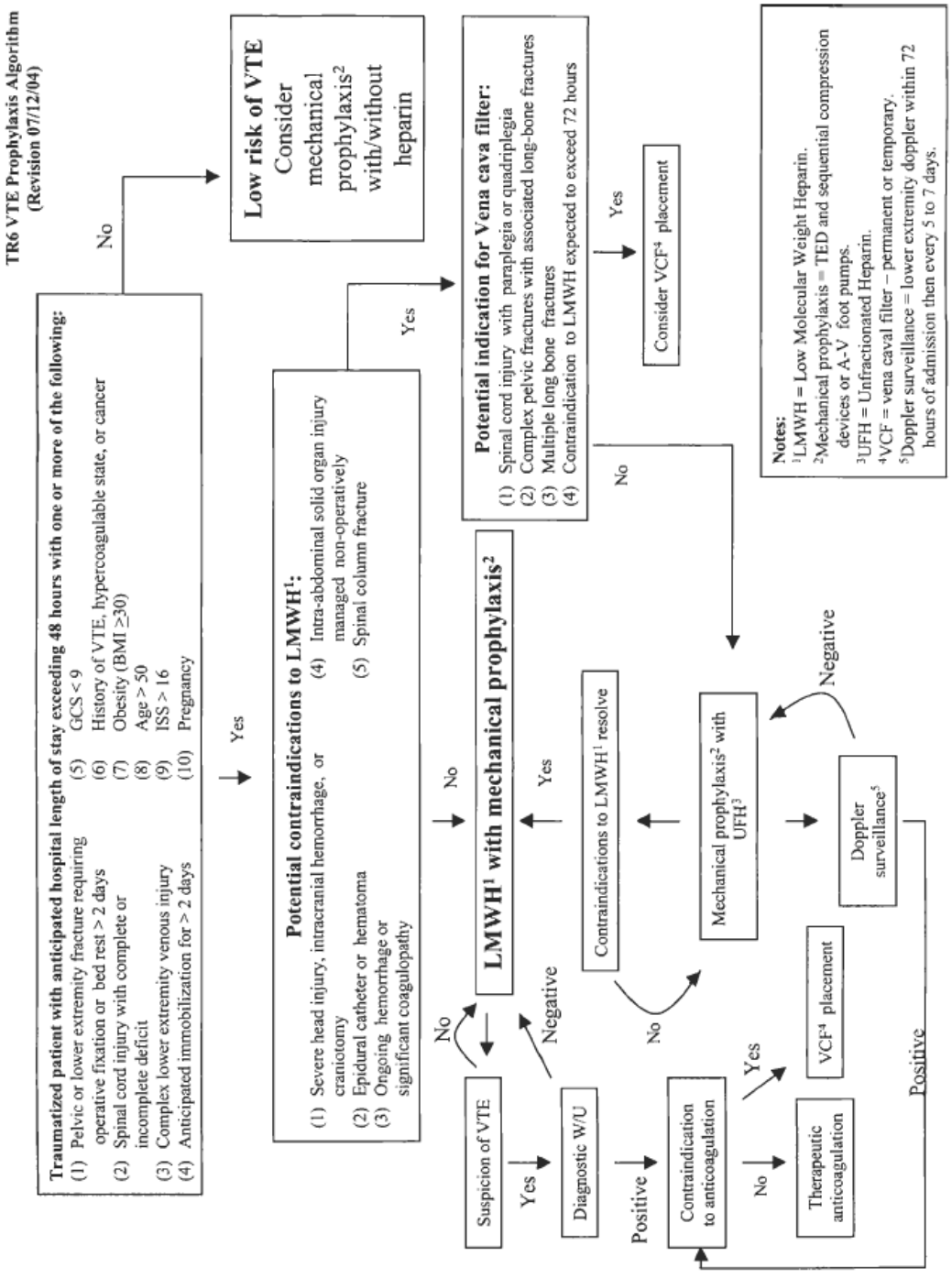
TR6: VTE prophylaxis Algorithm
(Revision 07/12/04)



TR7: Sedation Protocol Draft (07/12/04)

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Sedation/Analgesia Protocol for Mechanical Ventilation
Purpose: To provide a strategy for physician and nursing staffs to manage issues of sedation and analgesia in mechanically ventilated patients. These guidelines should direct the care of routine patients. They should be modified on the basis of clinical indication.

Goals: 1) Sedation level should be recorded using an objective scoring instrument (e.g. Ramsey, Riker, Richmond scales). 2.) Unless medically contraindicated, the optimal target level of sedation is that at which the patient is alert, not agitated, and able to maintain brief eye contact and/or follow simple instructions.

Indications: All ICU patients who are mechanically ventilated.

Monitor: Assess pain and sedation every 15 minutes until patient reaches desired level of sedation. Thereafter assess every 4 hours unless otherwise indicated.

Exceptions: Patients who are allergic to any of the following agents.

Sedation Vacation: Unless medically contraindicated, sedation should be interrupted daily until the patient is awake (establish eye contact and/or follow simple instructions), or until the patient becomes agitated or uncomfortable.

Analgesia for PAIN:
Fentanyl: bolus 25-200mcg IV q 5 min to achieve specified goal. If goal met, continue bolus doses q 30-60 min. If goal not met after 3 hours begin infusion at 50 mcg/hr. If goal not met in 1 hr, bolus with amount of current rate and increase infusion by 25 mcg/hr.

Sedation for ANXIETY: (choose one)
Lorazepam: Bolus 1-2 mg IV q 15 min prn. If goal met, continue bolus doses q 2-4hr prn. If goal not met within 3 hours begin scheduled doses at 4 mg IV q 6 hours and continue bolus doses. If goal not met in 24 hours, begin infusion at 2 mg/hr and continue bolus doses prn. If goal not met after 1 hour increase infusion rate by 1 mg/hr and continue boluses prn. Consider contribution of pain and delirium to agitation.

Propofol: (Consider use if expected duration of mechanical ventilation <48 hours, or for Neurosurgical patients). Bolus 0.5 mg/kg IV, then infuse20 mcg/kg/min. If goal not met in 15 minutes rebolus with 0 .5 mg/kg over 2 minutes and increase infusion by 10 mcg/kg/min q 15 min to maximum 100 mcg/kg/min. Consider contribution of pain and delirium to agitation.

Antipsychotic for DELIRIUM:
Haloperidol: 2-10 mg IV q 1 hr prn. If goal not met in 6 hours begin scheduled doses at 5 mg IV q 6 hrs and continue bolus doses.

References:
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Guidelines for Management of Traumatic Brain Injury
(Resuscitation Outcomes consortium)

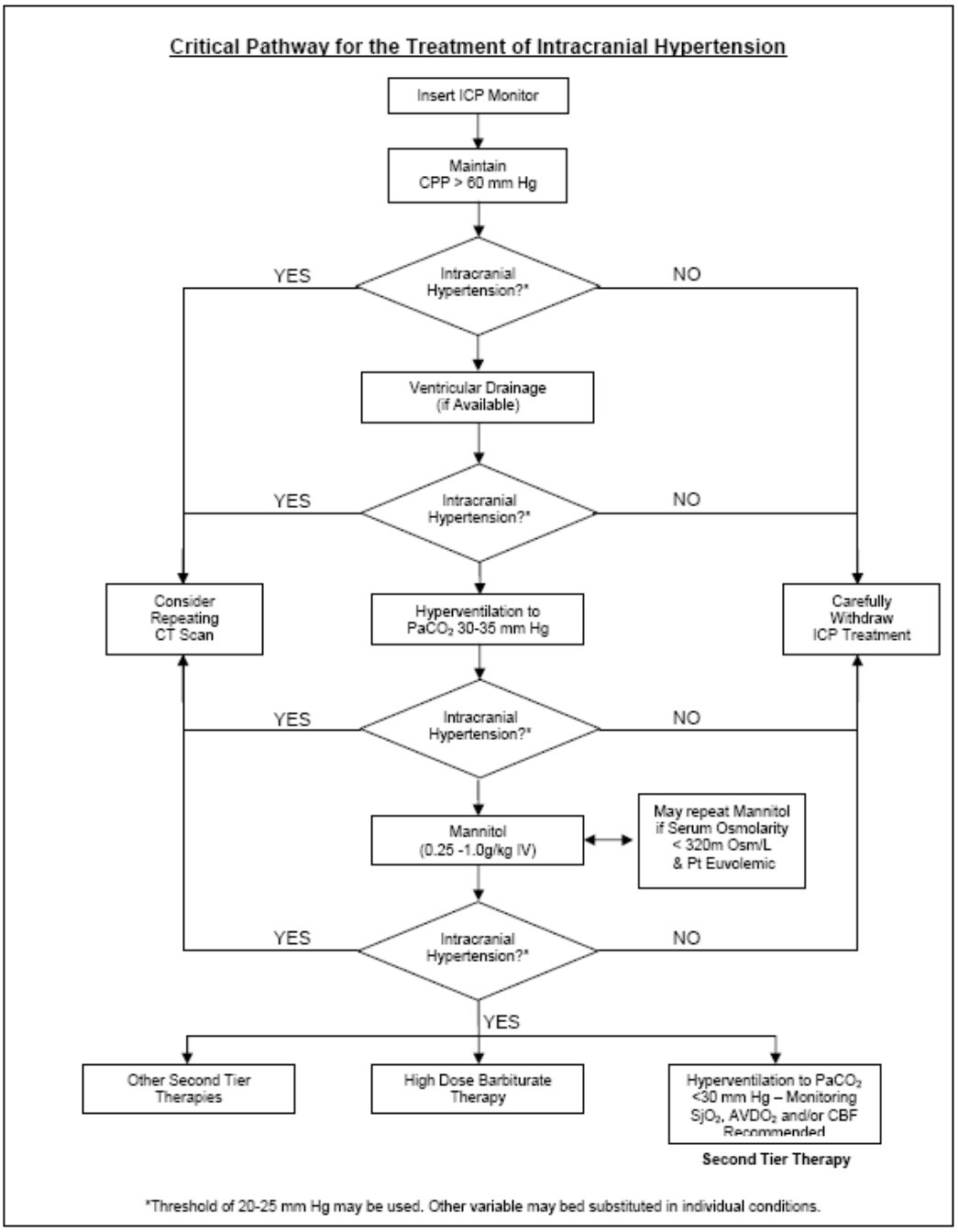
Monitoring & Management of Intracranial Pressure

All patients meeting the criteria for severe traumatic brain injury (persistent GCS <9) should have an intracranial pressure monitor placed.

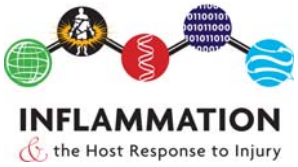
Patients with a sustained ICP>25mmHG should have intervention aimed at lowering ICP. This intervention is at the discretion of the treating physician but guided by the Brain Trauma Foundation Guidelines (See below). Excess hyperventilation should be avoided unless the patient is showing signs of acute herniation. Patients should be resuscitated to avoid episodes of hypotension (SBP<90 mmHg).

Brain Trauma Foundation Guidelines

The Brain Trauma Foundation, by consensus, has developed a critical pathway for the treatment of established intra-cranial hypertension, which is printed on the following page. It should be viewed as a framework that may be useful in guiding an approach to treating intracranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps.



Critical Pathway for the Treatment of Established Intracranial Hypertension in the severe head injury patient. Adapted from the Brain Trauma Foundation, Inc.

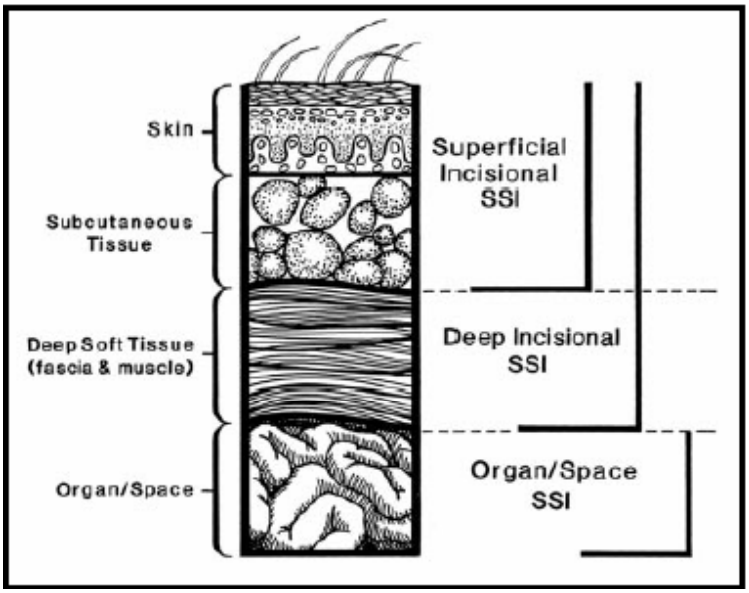


Infectious and Non-Infectious Complications —
Definitions from the Trauma-Related Database (TRDB)
Version Date: 10/22/2007

INFECTIOUS COMPLICATIONS – SUGICAL SITE INFECTIONS (SSI)

Surgical Site Infections

A surgical site is any site in which an incision has been made. As an example, an empyema occurring in a trauma patient without previous manipulation of the thorax is not a surgical site infection. It is an SSI if a chest tube (or VATS, thoracotomy) has been inserted/performed. The classification of SSI is based on the site of involvement.



Complications are selected from the list below. Definitions as well as diagnoses in the medical record are used to identify complications. Date of occurrence refers to date criteria are met.

SSI Type – Criteria for defining surgical site infections

Superficial Incisional SSI

Infection occurs within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infected burn wound.
3. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision *and* at least *one* of the following:

1. Purulent drainage from the deep incision, but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC), localized pain, or tenderness, unless site is culture-negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space (if the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.)
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

SSI Body Region, date and type of organism

If there are two organisms, list them both with the same date, type and region. It is possible to have more than one SSI involving the same body region over the course of hospitalization. If so, the events should be considered as two separate SSI with different dates, different types, but the same region. If two types of SSI occur together in the same region, on the same date, only the deepest infection is recorded. Date of onset is the date on which all criteria are met.

INFECTIOUS COMPLICATIONS: NON-SSI NOSOCOMIAL INFECTIONS

Nosocomial Infection Site, Date, and Organism

The date of infection refers to the date on which all criteria were met. Definitions as described below. For sites that have a bacterial threshold (e.g. BAL, UTI), record only those infections that exceed the threshold. For all other sites, record all infections. Continue to use these rules when cultures reveal multiple pathogens (record all infections present, according to criteria). A positive BAL is 10,000 organisms. A positive protected specimen brushing is 1000 organisms.

Pneumonia

Bacterial confirmation using invasive means is strongly encouraged for all ventilated patients. Additionally, the method of diagnosis (invasive/non-invasive) should be recorded.

Criteria a-c must be satisfied within a 48 hr period:

a) Radiologic criteria
   i. New radiographic infiltrate that persists for at least 24 hours
b) Clinical criteria (one of i or ii)
   i. Tm> 38.5°C or <35.0°C
   ii. WBC> 10,000 or < 3000 per cubic millimeter
c) Bacterial confirmation by at least one of:
   i. Quantitative microbiologic cultures obtained by bronchoalveolar lavage yielding≥10^4 colony forming units [CFU]/ml or protected specimen brush>10^3 CFU/ml (preferred diagnostic method)
   ii. Histopathologic exam of lung tissue shows one of a or b:
   (a). Abscess formation with intense PMN accumulation in bronchioles and alveoli.
   (b). Quantitative culture of lung parenchyma that shows $\geq$ 10^4 cfu/g tissue.
   iii. Positive blood culture for bacterial pathogen identified in sputum or respiratory culture
   iv. Positive pleural fluid culture with same organism identified in sputum or other respiratory culture
   v. Positive sputum gram stain with $\geq$3+ of one type of pathogenic bacteria
   vi. Heavy or moderate growth of one type of pathogenic bacteria on semi-quantitative sputum culture

Use bacterial confirmation methods iii, v, vi only if in the physician's notes it is documented that the patient has pneumonia AND is being treated with antimicrobial therapy. This only affects diagnoses by sputum cultures and does not affect cases where a BAL or protected specimen brush is performed.

Pneumonia Diagnosis Method

If both a sputum gram stain and BAL (or PSB) were done, then choose BAL or PSB.

Bloodstream Infections

Clinical criteria are required only if the organism identified is a common skin contaminant (diptheroids, Bacillus sp, Propionobacterium sp, coagulase-negative staphylococci)

a) Bacteriologic confirmation
   i. Recognized pathogen from one or more blood cultures and organism cultured is not related to an infection at another site
   ii. If a common skin contaminant as listed above, the organism must be cultured from at least two cultures within a 48 hour period
b) Clinical criteria (at least one of)

i. Fever>38.5 C
ii. WBC> 10,000 or < 3000 per cubic millimeter
iii. Hypotension (SBP<90) or >25% drop in systolic blood pressure

Catheter-Related Bloodstream Infections (CRBSI)
The presence of bacteremia/fungemia in a patient with a central venous catheter (CVC) in which there is no alternate source for bacteremia/fungemia except the catheter. To diagnose CRBSI, the patient must have clinical manifestations of infection; a positive blood culture from a peripheral vein; and some microbiologic evidence the catheter is infected.

Diagnostic criteria (all of 1, 2 and 3 must be met within a 48 hr period):

1. A single positive blood culture from a peripheral vein

2. Clinical manifestations of infection including at least one of a, b, or c
   a) Fever>38.5 C
   b) WBC> 10,000 or < 3000 per cubic millimeter
   c) Hypotension (SBP<90) or >25% drop in systolic blood pressure

3. Microbiologic evidence of catheter infection (at least one of a, b, c, or d)
   a) a positive semiquantitative (>15 CFU/catheter segment) culture in which the same organism is isolated from the catheter and peripheral blood (**this is the most commonly used technique)**
   b) a positive quantitative (>10^3 CFU/catheter segment catheter) culture in which the same organism is isolated from the catheter and peripheral blood
   c) simultaneous quantitative blood cultures with a $\geq$5:1 ratio of bacteria (CVC versus peripheral)
   d) differential period of central venous catheter culture versus peripheral blood culture positivity of >2 hours

Urinary Tract Infections
Criteria a and b must be satisfied within a 2-day period.
a) Clinical criteria (at least one of)
   i. Fever>38.5 C
   ii. WBC> 10,000 or < 3000 per cubic millimeter
   iii. Urgency
   iv. Dysuria
   v. Suprapubic tenderness
b) Bacterial confirmation
   vi. >10^5 organisms per ml of urine

Meningitis
Positive bacterial or fungal cultures from cerebrospinal fluid.

Sinusitis
Positive bacterial or fungal cultures from aspirate of sinuses obtained percutaneously or in the operating room.

Endocarditis
Evidence of vegetations on valve demonstrated on echocardiography or autopsy AND positive blood cultures.

Cholecystitis (Acalculous or Calculous)
Requires at least one of a or b:
a) Pathologic confirmation of acute cholecystitis
b) Ultrasound evidence of acute cholecystitis with at least one clinical criteria
    i. Fever>38.5 C
    ii. WBC> 10,000 or < 3000 per cubic millimeter

Empyema
Positive bacterial or fungal culture of fluid or tissue from pleural space requiring insertion of chest tube, percutaneous drainage or thoracoscopy/thoracotomy for evacuation and drainage

Pseudomembranous Colitis
May also be referred to as *Clostridium difficile* colitis. Requires clinical evidence of at least one of the following: (1) Pseudomembranes identified at lower gastrointestinal endoscopy; (2) Pathologic confirmation of pseudomembranous colitis; (3) *C. difficile* toxin detected in stool.

NON-INFECTIOUS COMPLICATIONS

The date refers to the date on which all criteria are met.

Acute Respiratory Distress Syndrome (ARDS)
Requires all of the three criteria below to be met within a 24-hour period.
a) Bilateral infiltrates (acute onset)
b) PaO2/FiO2<200 regardless of PEEP
c) No evidence of left atrial hypertension (PCWP≤18 if measured) or no evidence of congestive heart failure in the absence of a PAC. If a PAC is in place there must be evidence that the PCWP was ≤18 for at least 12 consecutive hours during the 24-hour assessment block

Fat Embolism Syndrome
Long bone fracture and development of at least 1 major and 3 minor OR 2 major and 2 minor criteria (as defined below) within 48 hrs of admission or within 24 hours of fixation of femur, fibula, tibia, or humerus.
a) Major signs
   i. Petechial rash
   ii. CNS depression – confusion, drowsiness coma not evident at admission
   iii. Respiratory symptoms: PaO2/FiO2<300 or bilateral diffuse patchy infiltrates on CXR
b) Minor signs
   i. Tachycardia>120 beats/min
   ii. Temperature>39.4
   iii. Retinal changes – fat or petechiae
   iv. Jaundice
   v. Anuria or oliguria (<30 cc's hour)
   vi. Thrombocytopenia >50% decrease over admission platelet count
   vii. Sudden decrease in hemoglobin/hematocrit>20%
   viii. Fat globules in urine or blood

Cardiac Arrest
Sudden cessation of cardiac activity AFTER ARRIVAL TO ED. Includes PEA (pulseless electrical activity).

Myocardial Infarction
Acute, irreversible myocardial injury documented by both of: (1) Abnormal increase in CK-MB or troponin and (2) New, serial T-wave, S-T segment or Q wave ECG abnormalities.

Cerebral Infarction
New neurologic deficit not present on admission which is sudden or rapid in onset and lasts>24 hrs or until death and confirmed as an infarction by CT or MRI.

Deep Venous Thrombosis (DVT)
Venous thrombosis confirmed by autopsy, venogram, duplex scan or other non-invasive vascular evaluation

Pulmonary Embolus
Requires at least one of the following:
a) Angiographic confirmation of pulmonary embolus
b) Computed tomography (CT) confirmation of pulmonary embolus
c) Moderate probability or high probability ventilation/perfusion radionuclide scan

Rhabdomyolysis
Requires one of the following:
a) Serum myoglobin>10,000 ng/ml
b) CK > 5000
AND one of the following:
c) Positive urinary myoglobin (qualitative or quantitative)
d) Urine that is positive for blood on dipstick (thus positive for heme) with no red blood cells
e) Renal dysfunction not explained by other insult

Abdominal Compartment Syndrome
Requires opening of abdominal cavity for elevated intra-abdominal pressure (>25 cm H20) associated with at least one of the following: oliguria (<30 cc's/hour), diminished cardiac output (<2.5 L/min/m2), elevated static pressures (>45 cmH20) or PaO2/FiO2 ratio of less than 200.

Upper Gastrointestinal Bleeding
Requires evidence of overt bleeding AND clinical symptoms (defined below) occurring later than 48 hrs following trauma.
Overt bleeding
a) Overt bleeding – any one of below
    i. Hematemesis, gross blood or coffee grounds in NG aspirate
    ii. Hematochezia
    iii. Melena
b) Clinical symptoms – any one of below
    i. Heart rate increase>20 beats/min
    ii. Blood pressure drop>20 mmHg
    iii. Hemoglobin drop> 2 g/dl (or hematocrit drop of >6 points) or requiring transfusion

Acute Lung Injury
Requires all of the three criteria below to be met within a 24-hour period.
a) Bilateral infiltrates (acute onset)
b) PaO2/FiO2<300 regardless of PEEP
c) No evidence of left atrial hypertension (PCWP≤18 if measured) or no evidence of congestive heart failure in the absence of a PAC. If a PAC is in place there must be evidence that the PCWP was ≤18 for at least 12 consecutive hours during the 24 hour assessment block

Appendix 3 PROPPR IB (AABB/Red Cross Guidelines)

CIRCULAR OF INFORMATION

FOR THE USE OF HUMAN BLOOD AND BLOOD COMPONENTS

This *Circular* was prepared jointly by AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program. The Food and Drug Administration recognizes this *Circular of Information* as an acceptable extension of container labels.

The online version of this *Circular of Information* is provided for educational purposes. It may not be modified in any way without the express permission of the AABB, ARC, ABC, and ASBP. Printed copies of the *Circular* are intended to accompany blood and blood components, and can be ordered through the AABB sales department or the online Bookstore. Please refer to this Web site's "Terms of Use" for additional information.

Federal Law prohibits dispensing the blood and blood components described in this circular without a prescription.

For printed copies, please order online at www.aabb.org/marketplace or call 1.866.222.2498.

Table of Contents

Notice to All Users

The *Circular of Information for the Use of Human Blood and Blood Components* (hereafter referred to as *Circular*) is an extension of container labels, as the space on those labels is limited.

Blood and blood components are biologic products and, in the form of cellular products, living human tissue intended for use in patient treatment. Professional judgment based on clinical evaluation determines the selection of components, dosage, rate of administration, and decisions in situations not covered in this general statement.

This *Circular*, as a whole or in part, cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described blood or blood components when used for their intended purpose. Attention to the specific indications for blood components is needed to prevent inappropriate transfusion.

Because of the risks associated with transfusion, physicians should be familiar with alternatives to allogeneic transfusion. Blood banks and transfusion services are referred to the AABB *Standards for Blood Banks and Transfusion Services* for additional information and policies, especially in the areas of recipient sample identification, compatibility testing, issue and transfusion of blood and blood components, investigation of transfusion reactions, and proper record-keeping practices. Transfusionists are referred to the AABB *Technical Manual* for applicable chapters on adult and pediatric transfusion.

The specific product manufacturer's package insert should be reviewed for instructions pertaining to use of transfusion devices (eg, filters, blood administration sets, and blood warmers).

This *Circular* is supplied to conform with applicable federal statutes and regulations of the Food and Drug Administration (FDA), United States (US) Department of Health and Human Services. The blood components in this *Circular* marked with the symbol "Ω" are blood components for which FDA currently has not received data to demonstrate that they meet prescribed requirements of safety, purity, and potency, and therefore are not licensed for distribution in interstate commerce.

General Information for Whole Blood and All Blood Components

Donors

Blood and blood components described in this *Circular* have been collected from volunteer blood donors for use in other patients (allogeneic transfusions) or from patients donating for themselves (autologous transfusions). The donors have been questioned about risk factors for transmissible infectious agents, have satisfactorily completed a health assessment that includes a questionnaire on past and present illnesses, have satisfied minimum physiologic criteria, and may have had the opportunity to confidentially exclude their donation from transfusion.

Testing of Donor Blood

Testing of a sample of donor blood is performed before units of blood or blood components are distributed for routine transfusion. The donor's ABO group and Rh type have been determined, including testing for the presence of weak D antigen.

A sample from each donation intended for allogeneic use has been tested by FDA-licensed tests and found to be nonreactive for antibodies to human immunodeficiency virus (anti-HIV-1/2), hepatitis C virus (anti-HCV), human T-cell lymphotropic virus (anti-HTLV-I/II), and hepatitis B core antigen (anti-HBc), and nonreactive for hepatitis B surface antigen (HBsAg).

Licensed nucleic acid tests (NAT) for HCV ribonucleic acid (RNA), HIV-1 RNA, and West Nile virus (WNV) RNA have been performed and found to be nonreactive. A serologic test for syphilis has been performed and found to be nonreactive.

For units labeled "FOR AUTOLOGOUS USE ONLY," infectious disease testing requirements vary depending on whether the unit will be drawn in one facility and infused in another facility and whether the unit might be made available for allogeneic transfusion. Infectious disease testing may be omitted for autologous units drawn, stored, and infused at the same facility. Autologous units for which testing has not been performed are labeled "DONOR UNTESTED." Autologous units with reactive test results may be used for transfusion to the donor-patient with appropriate physician authorization. A biohazard label will be applied to autologous units that are tested for evidence of infection as listed above and determined to be reactive. If the units labeled "FOR AUTOLOGOUS USE ONLY" are infused at a different facility, at a minimum the first donation from the donor-patient in each 30-day period is tested for evidence of infection as listed above. Subsequent units that are not tested will be labeled as "DONOR TESTED WITHIN THE LAST 30 DAYS." If an establishment allows any autologous donation to be available for allogeneic transfusion, or ships autologous donations to any establishment that does, the collecting establishment must test each donation for evidence of infection as listed above. This includes units labeled "FOR AUTOLOGOUS USE ONLY."

Tests for unexpected antibodies against red cell antigens have been performed on samples from all donors. The results of these tests are negative or have been determined to be clinically insignificant unless otherwise indicated on the label. Other tests may have been performed on donor blood as indicated by information that has been provided by the blood bank or transfusion service on an additional label or tie tag, or in a supplement to this *Circular*.

Blood and Component Labeling

All blood components identified in this *Circular* have the ISBT 128 product name listed first and other recognized component names in parentheses.

Blood and blood component labels will contain the following information:

1. The proper name, whole blood or blood component, including an indication of any qualification or modification.
2. The method by which the blood component was prepared, either by whole blood or apheresis collection.
3. The temperature range in which the blood component is to be stored.
4. The preservatives and anticoagulant used in the preparation of the blood or blood components, when appropriate.
5. The standard contents or volume is assumed unless otherwise indicated on the label or in *Circular* supplements.
6. The number of units in pooled blood components and any sedimenting agent used during cytapheresis, if applicable.
7. The name, address, registration number, and US license number (if applicable) of the collection and processing location.
8. The expiration date (and time if applicable), which varies with the method of preparation (open or closed system) and the preservatives and anticoagulant used. When the expiration time is not indicated, the product expires at midnight.
9. The donation (unit or pool) identification number.
10. The donor category (paid or volunteer, and autologous if applicable).
11. ABO group and Rh type, if applicable.
12. Special handling information, as required.
13. Statements regarding recipient identification, this *Circular*, infectious disease risk, and prescription requirement.

Instructions for Use

The following general instructions pertain to Whole Blood and all the blood components described in this *Circular:*

1. All blood and blood components must be maintained in a controlled environment and stored under appropriate conditions as described in the AABB *Standards for Blood Banks and Transfusion Services*.
2. The intended recipient and the blood container must be properly identified before the transfusion is started.
3. Aseptic technique must be employed during preparation and administration. If the container is entered in a manner that violates the integrity of the system, the component expires 4 hours after entry if maintained at room temperature (20-24 C), or 24 hours after entry if refrigerated (1-6 C).
4. All blood components must be transfused through a filter designed to remove clots and aggregates (generally a standard 170- to 260-micron filter).
5. Blood and blood components should be mixed thoroughly before use.
6. Blood and blood components must be inspected immediately before use. If, upon visual inspection, the container is not intact or the appearance is abnormal (presence of excessive hemolysis, a significant color change in the blood bag as compared with the tubing segments, floccular material, cloudy appearance, or other problems), the blood or blood component must not be used for transfusion and appropriate follow-up with the transfusion service must be performed.
7. No medications or solutions may be routinely added to or infused through the same tubing with blood or blood components with the exception of 0.9% Sodium Chloride, Injection (USP), unless 1) they have been approved for this use by the FDA or 2) there is documentation available to show that the addition is safe and does not adversely affect the blood or blood component.
8. Lactated Ringer's, Injection (USP) or other solutions containing calcium should never be added to or infused through the same tubing with blood or blood components containing citrate.
9. Blood components should be warmed if clinically indicated for situations such as exchange or massive transfusions, or for patients with cold-reactive antibodies. Warming must be accomplished using an FDA-cleared warming device so as not to cause hemolysis.
10. Some life-threatening reactions occur after the infusion of only a small volume of blood or blood components. Therefore, unless otherwise indicated by the patient's clinical condition, the rate of infusion should initially be slow.
11. Periodic observation and recording of vital signs should occur during and after the transfusion to identify suspected adverse reactions. If a transfusion reaction occurs, the transfusion must be discontinued immediately and appropriate therapy initiated. The infusion should not be restarted unless approved by transfusion service protocol.
12. Specific instructions concerning possible adverse reactions shall be provided to the patient or a responsible caregiver when direct medical observation or monitoring of the patient will not be available after transfusion.
13. Transfusion should be started before component expiration and completed within 4 hours.
14. All adverse events related to transfusion, including possible bacterial contamination of blood or a blood component or suspected disease transmission, must be reported to the transfusion service according to its local protocol.

Immunologic Complications, Immediate

1. *Hemolytic transfusion reaction*, the destruction of red cells, is discussed in detail in the section on components containing red cells and in the platelet section.
2. *Immune-mediated platelet destruction*, one of the causes of refractoriness to platelet transfusion, is the result of alloantibodies in the recipient to HLA or platelet-specific antigens on transfused platelets. This is described in more detail in the section on platelets.
3. *Febrile nonhemolytic reaction* is typically manifested by a temperature elevation of ≥1 C or 2 F occurring during or shortly after a transfusion and in the absence of any other pyrexic stimulus. This may reflect the action of antibodies against white cells or the action of cytokines, either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may occur in approximately 1% of transfusions, and they occur more frequently in patients receiving non-leukocyte-reduced platelets and those previously alloimmunized by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are caused by cytokines in the component, prestorage leukocyte reduction may be benefical.
4. *Allergic reactions* frequently occur as mild or self-limiting urticaria or wheezing that usually respond to antihistamines. More severe manifestations including respiratory and cardiovascular symptoms are more consistent with anaphylactoid/anaphylactic reactions and may require more aggressive therapy (see below). No laboratory procedures are available to predict these reactions.
5. *Anaphylactoid/anaphylactic reactions*, characterized by hypotension, tachycardia, nausea, vomiting and/or diarrhea, abdominal pain, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are rare but dangerous complications requiring immediate treatment with epinephrine. These reactions have been reported in IgA-deficient patients who develop IgA antibodies. Such patients may not have been previously transfused and may develop symptoms after infusion of very small amounts of IgA-containing plasma, in any blood component. Similar reactions have also been described in patients with haptoglobin deficiency. In certain circumstances, patients might benefit from the use of washed cellular components to prevent or reduce the severity of allergic reactions not minimized by treatment with medication alone.
6. *Transfusion-related acute lung injury* (TRALI) is the acute onset of hypoxemia within 6 hours of a blood or blood component transfusion and is the most commonly reported cause of transfusion-related deaths in the United States. In addition to hypoxemia, criteria for diagnosis include the presence of bilateral infiltrates on frontal chest radiographs and the exclusion of transfusion-associated circulatory overload (TACO), or preexisting acute lung injury. The exact mechanism of TRALI is not known, but hypotheses include donor antibodies that react against white cell antigens (HLA or human neutrophil antigens) and the sequestration of neutrophils by the pulmonary endothelium (caused by the recipient's underlying condition) that are subsequently activated by the infusion of substances in the donor plasma such as antibodies or other biologically active substances. In far fewer cases, antibodies in the recipient that may react with antigens on transfused white cells have been implicated. Laboratory testing does not alter management of this reaction, which is diagnosed

mainly on clinical and radiographic findings. Treatment of TRALI requires aggressive respiratory support, frequently requiring mechanical ventilation.

Immunologic Complications, Delayed

1. *Delayed hemolytic reaction* is described in detail in the section on components containing red cells.
2. *Alloimmunization* to antigens of red cells, white cells, platelets, or plasma proteins may occur unpredictably after transfusion. Blood components may contain certain immunizing substances other than those indicated on the label. For example, platelet components may also contain red cells and white cells. Primary immunization does not become apparent until days or weeks after the immunizing event, and does not usually cause symptoms or physiologic changes. If components that express the relevant antigen are subsequently transfused, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Clinically significant antibodies to red cell antigens will ordinarily be detected by pretransfusion testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can be detected only by specialized testing.
3. *Posttransfusion purpura* (PTP) is a rare syndrome characterized by the development of dramatic, sudden, and self-limited thrombocytopenia, typically 7 to 10 days after a blood transfusion, in a patient with a history of sensitization by either pregnancy or transfusion. Although the immune specificity may be to a platelet-specific antigen the patient lacks, both autologous and allogeneic platelets are destroyed. High-dose Immune Globulin, Intravenous (IGIV) may correct the thrombocytopenia.
4. *Transfusion-associated graft-vs-host disease* (TA-GVHD) is a rare but extremely dangerous condition that occurs when viable T lymphocytes in the transfused component engraft in the recipient and react against recipient tissue antigens. TA-GVHD can occur if the host does not recognize and reject the foreign transfused cells, and it can follow transfusion of any component that contains even very small numbers of viable T lymphocytes. Recipients with severe cellular immunodeficiency (except for HIV infection) are at greatest risk (eg, fetuses receiving intrauterine transfusions, recipients of hematopoietic progenitor cell transplants, and selected patients with severe immunodeficiency conditions), but TA-GVHD has also been reported in recipients receiving fludarabine for oncologic and rheumatologic diseases, and in immunologically normal recipients who are heterozygous for a tissue antigen haplotype for which the donor is homozygous. Tissue antigen haplotype sharing is most likely to occur when the transfused component is from a blood relative or has been selected for HLA compatibility. TA-GVHD remains a risk with leukocyte-reduced components because they contain sufficient residual T lymphocytes. Irradiation of the component renders T lymphocytes incapable of proliferation and is presently the only approved means to prevent TA-GVHD.

Nonimmunologic Complications

1. *Because whole blood and blood components are made from human blood, they may carry a risk of transmitting infectious agents [eg, viruses, bacteria, parasites, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the classic CJD agent].* Careful donor selection and available laboratory tests do not totally eliminate the hazard. Also, septic and toxic reactions can result from transfusion of bacterially contaminated blood and blood components. Such reactions are infrequent, but may be life-threatening. This may occur despite careful selection of donors and testing of blood. Donor selection criteria are designed to screen out potential donors with increased risk of infection with HIV, HTLV, hepatitis, and syphilis, as well as other agents (see section on Testing of Donor Blood). These procedures do not totally eliminate the risk of transmitting these agents.

Cytomegalovirus (CMV) may, unpredictably, be present in white-cell-containing components from donors previously infected with this virus, which can persist lifelong despite the presence of serum antibodies. Up to 70% of donors may be anti-CMV positive. Transmission of CMV by transfusion may be of concern in low-birthweight (≤1200 g) premature infants born to CMV-seronegative mothers and in certain other categories of immunocompromised individuals, if they are CMV seronegative. For at-risk recipients, the risk of CMV transmission by cellular components can be reduced by transfusing CMV-seronegative or leukocyte-reduced components.

For *other infectious agents* (eg, *Babesia* spp, *Leishmania* spp, and *Plasmodia* spp) there are no routinely available tests to predict or prevent disease transmission. All potential blood donors are subjected to screening procedures intended to reduce to a minimum the risk that they will transmit infectious agents.

2. *Bacterial sepsis* occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever (≥2 C or ≥3.5 F increase in temperature), severe chills, hypotension, or circulatory collapse during or shortly after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction. Although platelet components stored at room temperature have been implicated most frequently, previously frozen components thawed by immersion in a waterbath and red cell components stored for several weeks at 1 to 6 C have also been implicated. Although most apheresis platelets are routinely tested for bacterial contamination, this does not completely eliminate the risk.

   Both gram-positive and gram-negative organisms have been identified as causing septic reactions. Organisms capable of multiplying at low temperatures (eg, *Yersinia enterocolitica*) and those using citrate as a nutrient are most often associated with components containing red cells. A variety of pathogens, as well as skin contaminants, have been found in platelet components. Endotoxemia in recipients has resulted from multiplication of gram-negative bacteria in blood components.

   Prompt recognition of a possible septic reaction is essential, with immediate discontinuation of the transfusion and aggressive therapy with broad-spectrum antimicrobials and vasopressor agents, if necessary. In addition to prompt sampling of the patient's blood for cultures, investigation should include examination of material from the blood container by Gram's stain, and cultures of specimens from the container and the administration set. It is important to report all febrile transfusion reactions to the transfusion service. Follow-through from the transfusion service to the blood collection facility may facilitate retrieval of other components associated with the collection.

3. *TACO*, leading to pulmonary edema, can occur after transfusion of excessive volumes or at excessively rapid rates. This is a particular risk in the very young and the elderly and in patients with chronic severe anemia in whom low red cell mass is associated with high plasma volume. Small transfusion volumes can precipitate symptoms in at-risk patients who already have a positive fluid balance.

   Pulmonary edema should be promptly and aggressively treated, and infusion of colloid preparations, including plasma components and the suspending plasma in cellular components, reduced to a minimum.

4. *Hypothermia* carries a risk of cardiac arrhythmia or cardiac arrest and exacerbation of coagulopathy. Rapid infusion of large volumes of cold blood or blood components can depress body temperature, and the danger is compounded in patients experiencing shock or surgical or anesthetic manipulations that disrupt temperature regulation. A blood warming device should be considered if rapid infusion of blood or blood components is needed. Warming must be accomplished using an FDA-cleared warming device so as not to cause hemolysis.

5. *Metabolic complications* may accompany large-volume transfusions, especially in neonates and patients with liver or kidney disease.
   a. Citrate "toxicity" reflects a depression of ionized calcium caused by the presence in the circulation of large quantities of citrate anticoagulant. Because citrate is promptly metabolized by the liver, this complication is rare. Patients with severe liver disease or those with circulatory collapse that prevents adequate hepatic blood flow may have physiologically significant hypocalcemia after rapid, large-volume transfusion. Citrated blood or blood components administered rapidly through central intravenous access may reach the heart so rapidly that ventricular arrhythmias occur. Standard measurement of serum calcium does not distinguish ionized from complexed calcium. Ionized calcium testing or electrocardiogram monitoring is more helpful in detecting physiologically significant alteration in calcium levels.
   b. Other metabolic derangements can accompany rapid or large-volume transfusions, especially in patients with preexisting circulatory or metabolic problems. These include acidosis or alkalosis (deriving from changing concentrations of citric acid and its subsequent conversion to pyruvate and bicarbonate) and hyper- or hypokalemia.

Fatal Transfusion Reactions

When a fatality occurs as a result of a complication of blood or blood component transfusion, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), should be notified within 1 FDA business day (telephone: 301-827-6220; e-mail: fatalities2@fda.hhs.gov). Within 7 days after the fatality, a written report must be submitted to the Director, Office of Compliance and Biologics Quality, HFM-600, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. A copy of the report should be sent to the collecting facility, if appropriate. Updated information about CBER reporting requirements may be found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/default.htm.

Components Containing Red Cells

Overview

Description

Red cells contain hemoglobin and serve as the primary agent for transport of oxygen to tissues. The primary red-cell-containing transfusion component is Red Blood Cells (RBCs). This component is prepared by centrifugation or sedimentation of Whole Blood to remove much of the plasma. RBC components can also be prepared by apheresis methods.

Depending upon the collection system used, a single whole blood donation typically contains either 450 mL (±10%) or 500 mL (±10%) of blood collected from blood donors with a minimum hematocrit of 38%, withdrawn in a sterile container that includes an anticoagulant solution licensed for this component. Occasionally, units of other volumes are collected and those volumes are stated on the label.

Red-cell-containing components can be stored for an interval ("shelf life") determined by the properties of the anticoagulant-preservative solution (see Table 1). Whole Blood units are prepared in an aseptic manner in a ratio of 14 mL of anticoagulant-preservative solution per 100 mL of whole blood collected. Apheresis components are collected into anticoagulants as recommended by the manufacturer.

After plasma is removed, the resulting component is Red Blood Cells, which has a hematocrit of 65% to 80% and a usual volume between 225 mL and 350 mL. Additive solutions (AS) may

be mixed with the red cells remaining after removal of nearly all of the plasma (see Table 2). The typical hematocrit of AS RBCs is 55% to 65% and the volume is approximately 300 to 400 mL. AS RBCs have a shelf life of 42 days. Descriptions of specific components containing red cells are given at the end of this section.

Table 1. Contents of Anticoagulant-Preservative Solutions

Anticoagulant-Preservative	Trisodium Citrate	Citric Acid	Monobasic Sodium Phosphate	Dextrose	Adenine	Shelf Life
Anticoagulant citrate-dextrose A (ACD-A)*	22.0 g/L	8.0 g/L	0	24.5 g/L	0	21 days
Citrate-phosphate dextrose (CPD)	26.3 g/L	3.27 g/L	2.22 g/L	25.5 g/L	0	21 days
Citrate-phosphate-dextrose-dextrose (CP2D)	26.3 g/L	3.27 g/L	2.22 g/L	51.1 g/L	0	21 days
Citrate-phosphate-dextrose-adenine (CPDA-1)	26.3 g/L	3.27 g/L	2.22 g/L	31.9 g/L	0.275 g/L	35 days

*ACD is used for apheresis components.

Table 2. Content of Additive Solutions (in mg/100mL)

Additive Solution (mg/100 mL)	Dextrose	Adenine	Monobasic Sodium Phosphate	Mannitol	Sodium Chloride	Sodium Citrate	Citric Acid	Shelf Life
AS-1 (Adsol)	2200	27	0	750	900	0	0	42 days
AS-3 (Nutricel)	1100	30	276	0	410	588	42	42 days
AS-5 (Optisol)	900	30	0	525	877	0	0	42 days

Actions

All RBC components and Whole Blood increase the recipient's oxygen-carrying capacity by increasing the mass of circulating red cells. Processing and/or storage deplete the component of virtually all potential therapeutic benefit attributable to the functions of white cells and platelets; cellular elements remain in these blood components and may cause adverse immunologic or physiologic consequences. Residual plasma in the component provides the recipient with volume expansion and nonlabile plasma proteins to the extent that residual plasma is present in the preparation. Depending on the method of production, RBCs may contain approximately 20 to 100 mL of residual plasma. RBCs prepared with additive solutions are the most commonly used red cell product and have limited residual plasma.

Indications

Red-cell-containing components are indicated for treatment of symptomatic or critical deficit of oxygen-carrying capacity. They are also indicated for red cell exchange transfusion.

Contraindications

Red-cell-containing components should not be used to treat anemias that can be corrected with specific hematinic medications such as iron, vitamin B_{12}, folic acid, or erythropoietin.

RBCs or Whole Blood should not be used solely for volume expansion or to increase oncotic pressure of circulating blood.

Dosage and Administration

Each unit of RBCs or Whole Blood contains enough hemoglobin to increase the hemoglobin concentration in an average-sized adult by approximately 1 g/dL (increase hematocrit by 3%). Smaller aliquots can be made available for use with neonatal or pediatric patients, or adults with special transfusion needs.

The ABO group of all red-cell-containing components must be compatible with ABO antibodies in the recipient's plasma. Whole Blood must be ABO identical with the recipient; RBCs, which contain a reduced volume of antibody-containing plasma, need not be ABO identical.

Serologic compatibility between recipient and donor must be established before any red-cell-containing component is transfused. This may be accomplished by performing ABO/Rh typing, antibody screening, and crossmatching by serologic technique or use of a computer crossmatch. In cases when delay in transfusion will be life-threatening, uncrossmatched group O RBCs or ABO group-specific RBCs may be transfused before completion of pretransfusion compatibility testing.

The initial portion of each unit transfused should be infused cautiously and with sufficient observation to detect onset of acute reactions. Thereafter, the rate of infusion can be more rapid, as tolerated by the patient's circulatory system. It is undesirable for components that contain red cells to remain at room temperature longer than 4 hours. If the anticipated infusion rate must be so slow that the entire unit cannot be infused within 4 hours, it is appropriate to order smaller aliquots for transfusion.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the earlier section titled Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are hazards that apply specifically to components that contain red cells.

1. **Hemolytic transfusion reaction** is the immunologic destruction of transfused red cells, nearly always the result of incompatibility of antigen on the transfused cells with antibody in the recipient's circulation (see item 5 below for discussion of nonimmunologic hemolysis). The most common cause of severe, acute hemolytic reactions is transfusion of ABO-incompatible blood, resulting from identification errors occurring at some point(s) in the transfusion process. Serologic incompatibility undetected during pretransfusion testing is a much less common cause of acute hemolysis. If a transfusion reaction is suspected, the transfusion must be stopped and the transfusion service laboratory notified immediately. Information identifying the patient, the transfusion component, and associated forms and labels must be reviewed promptly to detect possible errors. A postreaction blood sample, preferably drawn from a site other than the transfusion access, must be sent to the laboratory along with the implicated unit of blood and administration set.

   Acute hemolytic reactions characteristically begin with an increase in temperature and pulse rate; symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock. Instability of blood pressure is frequent, the direction and magnitude of change depending upon the phase of the reaction and the magnitude of compensatory mechanisms. In anesthetized patients, hemoglobinuria, hypotension, and evidence of disseminated intravascular coagulopathy (DIC) may be the first signs of incompatibility. Laboratory

findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum bilirubin. The direct antiglobulin test (DAT) is usually positive, with rare exceptions (ie, complete hemolysis of incompatible red cells). Treatment includes measures to maintain or correct arterial blood pressure; correct coagulopathy, if present; and promote and maintain urine flow. Lack of symptoms does not exclude an acute hemolytic reaction.

Delayed hemolytic reactions occur in previously red-cell-alloimmunized patients in whom antigens on transfused red cells provoke anamnestic production of antibody. The anamnestic response reaches a significant circulating level while the transfused cells are still present in the circulation; the usual time frame is 2 to 14 days after transfusion. Signs may include unexplained fever, development of a positive DAT, and unexplained decrease in hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation of lactate dehydrogenase (LDH) or bilirubin may be noted. Most delayed hemolytic reactions have a benign course and require no treatment.

Hemolytic transfusion reactions in patients with sickle cell anemia may be particularly severe, with destruction of autologous as well as transfused red cells. In such patients, serologic investigations may not reveal the specificity of the causative antibody. Prospective matching for Rh and Kell antigens may decrease risk.

2. Antigens on transfused red cells may cause red cell **alloimmunization** of the recipient. Clinically significant antibodies to red cell antigens will usually be detected in pretransfusion antibody screening tests. For most patients, red cell antigen matching beyond ABO and Rh is unnecessary.
3. **TACO**, resulting in pulmonary edema, can accompany transfusion of any component at a rate more rapid than the recipient's cardiac output can accommodate. Whole Blood creates more of a risk than Red Blood Cells because the transfused plasma adds volume without increasing oxygen-carrying capacity. Patients with chronic anemia have increased plasma volumes and are at increased risk for circulatory overload.
4. **Iron overload** is a long-term complication of repeated RBC transfusions. Each transfusion contributes approximately 250 mg of iron. Patients requiring multiple transfusions for aplastic anemia, thalassemias, or hemoglobinopathies are at far greater risk than patients transfused for hemorrhagic indications, because blood loss is an effective means of iron excretion. Patients with predictably chronic transfusion requirements should be considered for treatment with iron-chelating agents or a program of exchange transfusion therapy, if applicable.
5. **Nonimmunologic hemolysis** occurs rarely, but can result from: 1) introduction of hypotonic fluids into the circulation, 2) effects of drugs co-administered with transfusion, 3) effects of bacterial toxins, 4) thermal injury to transfusion components, by either freezing or overheating, 5) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies, or 6) development of physical or osmotic stresses. Examples of situations capable of causing nonimmune red cell hemolysis include: exposure to excessive heat by non-FDA-approved warming methods, mixture with hypotonic solutions, or transfusion under high pressure through small-gauge or defective needles.

Components Available

1. **RED BLOOD CELLS (RED BLOOD CELLS)** are prepared from blood collected into any of the anticoagulant-preservative solutions approved by the FDA, and separated from the plasma by centrifugation or sedimentation. Separation may be done at any time during the allowable storage interval ("shelf life"). Red Blood Cells may contain from 160 to 275 mL of red cells (50-80 g of hemoglobin) suspended in varying quantities of residual plasma.

2. **RED BLOOD CELLS ADENINE SALINE ADDED (RED BLOOD CELLS ADENINE SALINE ADDED)** are prepared by centrifuging whole blood to remove as much plasma as possible, and replacing the plasma with usually 100 to 110 mL of an additive solution that contains some combination of dextrose, adenine, sodium chloride, and either monobasic sodium phosphate (AS-3) or mannitol (AS-1 and AS-5); the hematocrit is usually between 55% and 65%. Red Blood Cells in an additive solution have lower viscosity than Red Blood Cells, and flow through administration systems in a manner more comparable to that of Whole Blood. Red Blood Cells stored with an additive solution have an extended shelf life.
3. **RED BLOOD CELLS LEUKOCYTES REDUCED (RED BLOOD CELLS LEUKOCYTES REDUCED)** are prepared from a unit of Whole Blood (collected in anticoagulant-preservative solution as noted above) containing ≥1 to 10×10^9 white cells. In general, leukocyte reduction is achieved by filtration: 1) soon after collection (prestorage) or 2) after varying periods of storage in the laboratory. Leukocyte reduction will decrease the cellular content and volume of blood according to characteristics of the filter system used. RBCs Leukocytes Reduced must have a residual content of leukocytes $<5.0 \times 10^6$. Leukocyte reduction filters variably remove other cellular elements in addition to white cells. The leukocyte-reduced component contains at least 85% of the original red cell content.
4. **APHERESIS RED BLOOD CELLS (RED BLOOD CELLS PHERESIS)** are red cells collected by apheresis. This component must be collected in an approved anticoagulant. The red cell volume collected and the anticoagulant used are noted on the label. Aside from the automated collection method used, the component is comparable to whole-blood-derived RBCs in all aspects. The dosage can be calculated, as for RBCs, from the red cell content of the product. Apheresis RBCs contain on average 60 g of hemoglobin per unit.
5. **APHERESIS RED BLOOD CELLS LEUKOCYTES REDUCED (RED BLOOD CELLS PHERESIS LEUKOCYTES REDUCED)** are collected by apheresis methods. Leukocyte reduction is achieved in the manufacturing process resulting in a final product containing $<5.0 \times 10^6$ leukocytes and at least 85% of the target red cell content.
6. **RED BLOOD CELLS, LOW VOLUME (RED BLOOD CELLS, LOW VOLUME)** are products prepared when 300 to 404 mL of whole blood is collected into an anticoagulant volume calculated for 450 mL ± 45 mL or when 333 to 449 mL of whole blood is collected into an anticoagulant volume calculated for 500 mL ± 50 mL. These products reflect a collection with an altered ratio of anticoagulant to red cells and may not be an indication of a lower dose of hemoglobin. Plasma and platelet components should not be prepared from low-volume collections.
7. **WHOLE BLOOD (WHOLE BLOOD)** is rarely used for transfusion. In situations where Whole Blood is indicated but RBCs are used, a suitable plasma volume expander should be administered. See also General Information for Whole Blood and All Blood Components, Instructions for Use. All whole blood transfusions must be ABO identical.
8. **FROZEN RED BLOOD CELLS (RED BLOOD CELLS FROZEN)** and **FROZEN REJUVENATED RED BLOOD CELLS (RED BLOOD CELLS REJUVENATED FROZEN)** are prepared by adding glycerol to red cells as a cryoprotective agent before freezing. The glycerol must be removed from the thawed component before it is infused. Frozen RBCs may be stored for up to 10 years, and for longer intervals if there is particular need for specific units. Ω Frozen storage is especially suitable for red cells with unusual antigenic phenotypes.
9. **DEGLYCEROLIZED RED BLOOD CELLS (RED BLOOD CELLS DEGLYCEROLIZED)** is the form in which cryopreserved red cells (Frozen Red Blood Cells) are made available for infusion. Glycerol is added to red cells as a cryoprotective agent before freezing, and must be removed from the thawed component before it is infused.

Deglycerolized RBCs contain 80% or more of the red cells present in the original unit of blood, and have approximately the same expected posttransfusion survival as RBCs. Glycerol is removed by washing the cells with successively lower concentrations of Sodium Chloride, Injection (USP); the final suspension is in 0.9% Sodium Chloride, Injection (USP), with or without small amounts of dextrose. Small amounts of residual-free hemoglobin may cause the supernatant fluid to be pink-tinged.

Deglycerolized RBCs provide the same physiologic benefits as RBCs, but their use is usually restricted to situations in which standard transfusion components are inappropriate or unavailable. Deglycerolized RBCs may be useful for transfusions to patients with previous severe allergic transfusion reactions, because the process efficiently removes plasma constituents.

In addition to the side effects and hazards of RBC transfusion, Deglycerolized RBCs carry a risk of intravascular hemolysis if deglycerolization has been inadequate.

Deglycerolized RBCs must be transfused within 24 hours after thawing if prepared in an open system. If prepared in a closed system, they can be infused within a 2-week interval after thawing.

10. **REJUVENATED RED BLOOD CELLS (RED BLOOD CELLS REJUVENATED)** may be prepared from red cells stored in CPD, CPDA-1, and AS-1 storage solutions up to 3 days after expiration. Addition of an FDA-approved solution containing inosine, phosphate, and adenine restores 2,3-diphosphoglycerate and adenosine triphosphate to levels approximating those of freshly drawn cells. These products must be washed before infusion to remove the inosine, which may be toxic. Rejuvenated RBCs may be prepared and transfused within 24 hours or frozen for long-term storage.
11. **DEGLYCEROLIZED REJUVENATED RED BLOOD CELLS (RED BLOOD CELLS REJUVENATED DEGLYCEROLIZED)** is the form in which rejuvenated, cryopreserved red cells (Frozen Rejuvenated Red Blood Cells) are made available for infusion. For additional information, see sections on Rejuvenated RBCs and Deglycerolized RBCs above.
12. **Autologous Whole Blood and RBCs** are drawn from patients who anticipate requiring blood transfusions. Donor-safety screening criteria and testing procedures applicable to collection from allogeneic donors do not always apply to these components. Each unit must be labeled "FOR AUTOLOGOUS USE ONLY." A biohazard label is required if these units have a reactive test result. In addition, if these units are untested, they must be labeled as "DONOR UNTESTED." Autologous Whole Blood or RBCs can be modified into any of the components described above. If a facility allows for autologous units to be crossed over for inclusion in the general blood inventory, the donors and units must be subjected to the same donor eligibility requirements and test requirements as allogeneic donors and units.
13. See section on Further Processing for irradiated products.

Plasma Components

Overview

Plasma is the aqueous part of blood and can be derived from the separation of a whole-blood collection or by apheresis collection. Important elements in plasma include albumin, coagulation factors, fibrinolytic proteins, immunoglobulin, and other proteins. Once plasma is collected, it can be stored frozen and subsequently thawed and kept in a liquid state. If Fresh Frozen Plasma (FFP) is thawed at 1 to 6 C, and the insoluble cryoprecipitate (see Cryoprecipitated Components) is removed by centrifugation, the supernatant plasma can be refrozen and labeled as Plasma Cryoprecipitate Reduced. Labile coagulation factor levels vary based upon ABO group, storage conditions, and/or further processing (see Table 3).

Table 3. Coagulation Factor Activity of Thawed Plasma Derived from FFP*

Coagulation Factor	Level†					Mean Change from Day 1 to Day 5 (%)	p Values
	Day 1	Day 2	Day 3	Day 4	Day 5		
Factor VIII (%)							
Blood group A	107 ± 26	76 ± 19	66 ± 18	65 ± 17	63 ± 16	41	<0.004‡
Blood group B	103 ± 44	74 ± 37	71 ± 35	67 ± 36	67 ± 33	35	<0.02‡
Blood group O	70 ± 16	51 ± 10	43 ± 10	43 ± 7	41 ± 8	41	<0.001‡
Factor II (%)	81 ± 9	81 ± 9	81 ± 9	80 ± 10	80 ± 10	1	NS
Factor V (%)	79 ± 7	75 ± 8	71 ± 9	68 ± 9	66 ± 9	16	NS
Factor VII (%)	90 ± 18	81 ± 15	76 ± 15	72 ± 14	72 ± 15	20	NS
Factor X	85 ± 13	84 ± 13	84 ± 15	82 ± 11	80 ± 11	6	NS
Fibrinogen (mg/dL)	225 ± 12	224 ± 13	224 ± 13	224 ± 17	225 ± 12	0	NS

*Reported with permission from Downes KA, Wilson E, Yomtovian R, Sarode R. Serial measurement of clotting factors in thawed plasma for 5 days (letter). Transfusion 2001;41:570.
†Mean ± SD.
‡Comparison of Factor VIII activity at Day 1 and that at Day 3 was statistically significant.

Fresh Frozen Plasma

Description

FRESH FROZEN PLASMA (FRESH FROZEN PLASMA) is prepared from a whole blood or apheresis collection and frozen at –18 C or colder within the time frame as specified in the directions for use for the blood collection, processing, and storage system. The anticoagulant solution used and the component volume are indicated on the label. On average, units contain 200 to 250 mL, but apheresis-derived units may contain as much as 400 to 600 mL. FFP contains plasma proteins including all coagulation factors. FFP contains high levels of the labile coagulation Factors V and VIII.

FFP should be infused immediately after thawing or stored at 1 to 6 C for up to 24 hours. If stored longer than 24 hours, the component must be relabeled (see Thawed Plasma) or discarded depending on the method of collection.

Action

FFP serves as a source of plasma proteins for patients who are deficient in or have defective plasma proteins.

Indications

FFP is indicated in the following conditions:

1. Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (eg, liver disease, DIC).
2. Patients undergoing massive transfusion who have clinically significant coagulation deficiencies.
3. Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect.
4. For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).

5. Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available.
6. Management of patients with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable.

Contraindications

Do not use this product when coagulopathy can be corrected more effectively with specific therapy, such as vitamin K, Cryoprecipitated AHF (Antihemophilic Factor), or specific coagulation factor concentrates.

Do not use this product when blood volume can be safely and adequately replaced with other volume expanders.

Dosage and Administration

Compatibility tests before transfusion are not necessary. Plasma must be ABO compatible with the recipient's red cells. The volume transfused depends on the clinical situation and patient size, and may be guided by laboratory assays of coagulation function.

Do not use FFP if there is evidence of container breakage or of thawing during storage. FFP must be thawed in a waterbath at 30 to 37 C or in an FDA-cleared device. If a waterbath is used, thaw the component in a protective plastic overwrap using gentle agitation.

Side Effects and Hazards

Hazards that pertain to all transfusion components, including FFP, are described in the earlier section on Side Effects and Hazards for Whole Blood and All Blood Components.

Plasma Frozen Within 24 Hours After Phlebotomy

Description

PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY (PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY) is prepared from a whole blood collection and must be separated and placed at –18 C or below within 24 hours from whole blood collection. The anticoagulant solution used and the component volume are indicated on the label. On average, units contain 200 to 250 mL. This plasma component is a source of nonlabile plasma proteins. Levels of Factor VIII are significantly reduced and levels of Factor V and other labile plasma proteins are variable compared with FFP.

Plasma Frozen Within 24 Hours After Phlebotomy should be infused immediately after thawing or stored at 1 to 6 C for up to 24 hours. If stored longer than 24 hours, the component must be relabeled (see Thawed Plasma) or discarded.

Action

This plasma component serves as a source of plasma proteins for patients who are deficient in or have defective plasma proteins. Coagulation factor levels might be lower than those of FFP, especially labile coagulation Factors VIII and V.

Indications

See Fresh Frozen Plasma.

Contraindications

See Fresh Frozen Plasma. In addition, this product is not indicated for treatment of deficiencies of labile coagulation factors including Factors VIII and V.

Dosage and Administration

See Fresh Frozen Plasma.

Side Effects and Hazards

See Fresh Frozen Plasma.

Plasma Cryoprecipitate Reduced

Description

PLASMA CRYOPRECIPITATE REDUCED (PLASMA, CRYOPRECIPITATE REDUCED) is prepared from FFP after thawing and centrifugation and removal of the cryoprecipitate. The remaining product is plasma that is deficient in fibrinogen, Factor VIII, Factor XIII, von Willebrand factor (vWF), cryoglobulin, and fibronectin. This supernatant plasma must be refrozen within 24 hours. Proteins such as albumin; ADAMTS13; and Factors II, V, VII, IX, X, and XI remain in almost the same levels as in FFP [the high-molecular-weight forms of vWF (multimers) are more thoroughly removed by this process than smaller multimers].

Action

This component serves as a source for plasma proteins except for fibrinogen, Factor VIII, Factor XIII, and vWF.

Indications

Plasma Cryoprecipitate Reduced is used for transfusion or plasma exchange in patients with TTP. It may be used to provide clotting factors except fibrinogen, Factor VIII, Factor XIII, and vWF.

Contraindications

This component should not be used as a substitute for FFP, Plasma Frozen Within 24 Hours After Phlebotomy, or Thawed Plasma.

Dosage and Administration

See Fresh Frozen Plasma.

Side Effects and Hazards

See Fresh Frozen Plasma.

Liquid Plasma Components

Description

Other plasma components may be made from whole blood collected in all approved anticoagulants. Levels and activation state of coagulation proteins in these products are variable. The volume is indicated on the label.

THAWED PLASMA Ω (THAWED PLASMA) is derived from FFP or Plasma Frozen Within 24 Hours After Phlebotomy, prepared using aseptic techniques (closed system), thawed at 30 to 37 C, and maintained at 1 to 6 C for up to 4 days after the initial 24-hour post-thaw period has elapsed. The volume is indicated on the label. Thawed Plasma contains stable coagulation factors such as Factor II and fibrinogen in concentrations similar to those of FFP, but variably reduced amounts of other factors (see Table 3).

Action

This component serves as a source of plasma proteins. Levels and activation state of coagulation proteins in thawed plasma are variable and change over time.

Indications

1. Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors except for patients with a consumptive coagulopathy.
2. Initial treatment of patients undergoing massive transfusion who have clinically significant coagulation deficiencies.
3. Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect.

This component should not be used to treat isolated coagulation factor deficiencies where other products are available with higher concentrations of the specific factor(s).

Contraindications

See Fresh Frozen Plasma. Do not use liquid plasma components as the treatment for isolated coagulation factor deficiencies where other products are available with higher concentrations of the specific factor(s).

Dosage and Administration

See Fresh Frozen Plasma.

Side Effects and Hazards

See Fresh Frozen Plasma.

LIQUID PLASMA (LIQUID PLASMA) is separated no later than 5 days after the expiration date of the Whole Blood and is stored at 1 to 6 C. The profile of plasma proteins in Liquid Plasma is poorly characterized. Levels and activation state of coagulation proteins in Liquid Plasma are dependent upon and change with time in contact with cells, as well as the conditions and duration of storage.

Action

This component serves as a source of plasma proteins. Levels and activation state of coagulation proteins are variable and change over time.

Indications

Initial treatment of patients who are undergoing massive transfusion because of life-threatening trauma/hemorrhages and who have clinically significant coagulation deficiencies.

Contraindications

See Fresh Frozen Plasma. Do not use liquid plasma components as the treatment for isolated coagulation factor deficiencies where other products are available with higher concentrations of the specific factor(s).

Dosage and Administration

See Fresh Frozen Plasma.

Side Effects and Hazards

See Fresh Frozen Plasma.

Cryoprecipitated Components

Overview

Description

Cryoprecipitated Antihemophilic Factor (AHF) is prepared by thawing whole-blood-derived FFP between 1 and 6 C and recovering the precipitate. The cold-insoluble precipitate is refrozen within 1 hour. Cryoprecipitated AHF contains fibrinogen, Factor VIII, Factor XIII, vWF, and fibronectin. Each unit of Cryoprecipitated AHF should contain ≥80 IU Factor VIII units and ≥150 mg of fibrinogen in approximately 5 to 20 mL of plasma.

If the label indicates "Pooled Cryoprecipitated AHF," several units of Cryoprecipitated AHF have been pooled. The volume of the pool is indicated on the label and, if used, the volume of 0.9% Sodium Chloride, Injection (USP) added may be separately listed. To determine the minimum potency of this component, assume 80 IU of Factor VIII and 150 mg of fibrinogen for each unit of Cryoprecipitated AHF indicated on the label.

Action

Cryoprecipitate serves as a source of fibrinogen, Factor VIII, Factor XIII, vWF, and fibronectin.

Indications

This component is used in the control of bleeding associated with fibrinogen deficiency and to treat Factor XIII deficiency. It is also indicated as second-line therapy for von Willebrand disease and hemophilia A (Factor VIII deficiency). Coagulation factor preparations other than cryoprecipitate are preferred when blood component therapy is needed for management of von Willebrand disease and Factor VIII deficiency. Use of this component may be considered for control of uremic bleeding after other modalities have failed. Indications for use as a source of fibronectin are not clear.

Contraindications

Do not use this component unless results of laboratory studies indicate a specific hemostatic defect for which this product is indicated. Cryoprecipitate should not be used if virus-inactivated Factor VIII concentrates or recombinant factor preparations are available for management of patients with von Willebrand disease or hemophilia A.

Dosage and Administration

Compatibility testing is unnecessary. ABO-compatible material is preferred. Rh type need not be considered when using this component.

The frozen component is thawed in a protective plastic overwrap in a waterbath at 30 to 37 C up to 15 minutes (thawing time may need to be extended if product is pooled before freezing). This component should not be given if there is evidence of container breakage or of thawing during storage. Do not refreeze after thawing. Thawed Cryoprecipitated AHF should be kept at room temperature and transfused as soon as possible after thawing, within 6 hours if it is a single unit (from individual donor, or pooled before freezing or administration using an FDA-cleared sterile connecting device), and within 4 hours after entering the container (eg, to attach an administration set or to pool) without using an FDA-cleared sterile connecting device.

Cryoprecipitated AHF may be transfused as individual units or pooled. For pooling, the precipitate in one or more concentrates should be mixed well with 10 to 15 mL of diluent to ensure complete removal of all material from the container. The preferred diluent is 0.9%

Sodium Chloride, Injection (USP). Serial use of each bag's contents to resuspend the precipitate into subsequent bags may be used to efficiently pool cryoprecipitate into a single bag.

The recovery of transfused fibrinogen is 50% to 60%. When used to correct hypofibrinogenemia, Cryoprecipitated AHF may be dosed according to the following formula to raise plasma fibrinogen by approximately 50 to 100 mg/dL: Number of bags = 0.2 × body weight in kg. Thrombosis alters fibrinogen kinetics; therefore, patients receiving cryoprecipitate as fibrinogen replacement in conditions associated with increased fibrinogen turnover should be monitored with fibrinogen assays.

For treatment of bleeding in patients with hemophilia A when Factor VIII concentrates are not available, rapid infusion of a loading dose expected to produce the desired level of Factor VIII is usually followed by a smaller maintenance dose every 8 to 12 hours. To maintain hemostasis after surgery, a regimen of therapy for 10 days or longer may be required. If circulating antibodies to Factor VIII are present, the use of larger doses, activated concentrates, porcine-derived concentrates, or other special measures may be indicated. To calculate cryoprecipitate dosage as a source of Factor VIII, the following formula is helpful: Number of bags = (Desired increase in Factor VIII level in % × 40 × body weight in kg) / average units of Factor VIII per bag, minimum 80. Good patient management requires that the Cryoprecipitated AHF treatment responses of Factor VIII-deficient recipients be monitored with periodic plasma Factor VIII assays.

For treatment of von Willebrand disease, smaller amounts of Cryoprecipitated AHF will correct the bleeding time. Because the vWF content of Cryoprecipitated AHF is not usually known, an empiric dose of 1 bag per 10 kg of body weight has been recommended. These patients should be monitored by appropriate laboratory studies to determine the frequency of Cryoprecipitated AHF administration.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the earlier section on Side Effects and Hazards for Whole Blood and All Blood Components.

If a large volume of ABO-incompatible cryoprecipitate is used, the recipient may develop a positive DAT and, very rarely, mild hemolysis.

Components Available

1. **CRYOPRECIPITATED AHF (CRYOPRECIPITATED AHF)**
2. **POOLED CRYOPRECIPITATED AHF (CRYOPRECIPITATED AHF, POOLED)**

Platelet Components

Overview

Description

Platelet therapy may be achieved by infusion of either Apheresis Platelets or Platelets (whole-blood-derived platelet concentrates). In either component, platelets are suspended in an appropriate volume of the original plasma, which contains near-normal levels of stable coagulation factors that are stored at room temperature. One unit of Platelets derived from a whole blood collection usually contains no fewer than 5.5×10^{10} platelets suspended in 40 to 70 mL of plasma. Platelets may be provided either singly or as a pool. One unit of Apheresis Platelets usually contains $\geq 3.0 \times 10^{11}$ platelets and is a therapeutic equivalent to 4 to 6 units of

Platelets. Platelet components may contain a varying number of leukocytes depending upon the technique used in preparation. Some units may contain more than the trace amounts of red cells usually present and will appear pink to salmon in color.

Actions

Platelets are essential for normal hemostasis. Complex reactions occur between platelets, vWF, collagen in the walls of disturbed vasculature, phospholipids, and soluble coagulation factors, including thrombin. These changes induce platelet adherence to vessel walls and platelet activation, which leads to platelet aggregation and formation of a primary hemostatic plug. The therapeutic goal of platelet transfusion is to provide adequate numbers of normally functioning platelets for the prevention or cessation of bleeding.

Indications

Platelet transfusions may be given to patients with thrombocytopenia, dysfunctional platelet disorders, active platelet-related bleeding, or serious risk of bleeding (ie, prophylactic use). Patients with the following medical conditions may require platelet transfusion: leukemia, myelodysplasia, aplastic anemia, solid tumors, congenital or acquired platelet dysfunction, central nervous system trauma. Patients undergoing extracorporeal membrane oxygenation or cardiopulmonary bypass may also need platelet transfusion. Thrombocytopenia is unlikely to be the cause of bleeding in patients with platelet counts of at least 50,000/μL. Higher transfusion thresholds may be appropriate for patients with platelet dysfunction. For the clinically stable patient with an intact vascular system and normal platelet function, prophylactic platelet transfusions may be appropriate at 5000 to 10,000/μL.

Prophylactic platelet transfusion may not be of therapeutic benefit when thrombocytopenia is related to destruction of circulating platelets secondary to autoimmune disorders [eg, immune thrombocytopenic purpura (ITP)]; however, when these patients bleed, platelet therapy is often useful.

Platelets Leukocytes Reduced or Apheresis Platelets Leukocytes Reduced are indicated to decrease the frequency of recurrent febrile, nonhemolytic transfusion reaction, HLA alloimmunization, and transfusion-transmitted CMV infection (see section on Further Processing).

Contraindications

Do not use this component if bleeding is unrelated to decreased numbers of, or abnormally functioning, platelets. If platelet function is normal, platelets should not be transfused when the platelet count is greater than 100,000/μL. Prophylactic transfusion is generally not indicated when platelet dysfunction is extrinsic to the platelet, such as in uremia, certain types of von Willebrand disease, and hyperglobulinemia. Patients with congenital surface glycoprotein(s) defects should be transfused conservatively to reduce the possibility for alloimmunization to the missing protein(s).

Do not use in patients with activation or autoimmune destruction of endogenous platelets, such as in heparin-induced thrombocytopenia (HIT), TTP, or ITP, unless the patient has a life-threatening hemorrhage.

Dosage and Administration

Compatibility testing is not necessary in routine platelet transfusion. Except in unusual circumstances, the donor plasma should be ABO compatible with the recipient's red cells when this component is to be transfused to infants or when large volumes are to be transfused. The number of platelet units to be administered depends on the clinical situation of each patient. One unit of Platelets would be expected to increase the platelet count of a 70-kg adult by 5000 to

10,000/μL and increase the count of an 18-kg child by 20,000/μL. The therapeutic adult dose is 1 unit of Apheresis Platelets or 4 to 6 units of whole-blood-derived platelets, either of which usually contain $\geq 3.0 \times 10^{11}$ platelets. For prophylaxis, this dose may need to be repeated in 1 to 3 days because of the short lifespan of transfused platelets (3-4 days). Platelet components must be examined before administration. Units with excessive aggregates should not be administered. Transfusion may proceed as quickly as tolerated, but must take less than 4 hours. Do not refrigerate platelets.

The corrected count increment (CCI) is a calculated measure of patient response to platelet transfusion that adjusts for the number of platelets infused and the size of the recipient, based upon body surface area (BSA)

$$\text{CCI} = (\text{post-count} - \text{pre-count}) \times \text{BSA} / \text{platelets transfused}$$

where post-count and pre-count are platelet counts (/μL) after and before transfusion, respectively; BSA is the patient body surface area (meter^2); and platelets transfused is the number of administered platelets ($\times 10^{11}$). The CCI is usually determined 10 to 60 minutes after transfusion. For example:

A patient with acute myelogenous leukemia with a nomogram-derived BSA of 1.40 meter^2 is transfused with a unit of Apheresis Platelets (a platelet dose of 4.5×10^{11}). The pretransfusion platelet count is 2000/μL. The patient's platelet count from a sample of blood collected 15 minutes after platelet transfusion is 29,000/μL. The CCI is calculated as $(29{,}000 - 2000) \times 1.4 / 4.5 = 8{,}400$/μL per 10^{11} per m^2.

In the clinically stable patient, the CCI is typically greater than 7500 at 10 minutes to 1 hour after transfusion and remains above 4500 at 24 hours. Both immune and nonimmune mechanisms may contribute to reduced platelet recovery and survival. Along with supportive serologic test results, a CCI of less than 5000 at 10 minutes to 1 hour after transfusion may indicate an immune-mediated refractory state to platelet therapy. With nonimmune mechanisms, platelet recovery within 1 hour may be adequate, although survival at 24 hours is reduced (refer to Platelet Alloimmunization).

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the section on Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are hazards that apply specifically to components that contain platelets.

1. **Bacterial Contamination:** Although methods to limit and detect bacterial contamination have been implemented for most platelet components, they remain the most likely blood components to be contaminated with bacteria. Gram-positive skin flora are the most commonly recovered bacteria. Symptoms may include high fever (≥2.0 C or ≥3.5 F increase in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion. In some instances, symptoms, especially when associated with contamination by gram-positive organisms, may be delayed for several hours following transfusion. Prompt management should include broad-spectrum antibiotic therapy along with cultures from the patient, suspected blood component(s), and administration set. A Gram's stain of suspected contaminated unit(s) should be performed whenever possible. Apheresis Platelets are usually tested for bacterial contamination before issue.
2. **Platelet Alloimmunization:** Platelets bear a variety of antigens, including HLA and platelet-specific antigens. Patients transfused with platelets often develop HLA antibodies. The patient may become refractory to incompatible platelets. When platelets are transfused to a patient with an antibody specific for an expressed antigen, the survival time of the transfused

platelets may be markedly shortened. Nonimmune events may also contribute to reduced platelet survival. It is possible to distinguish between immune and nonimmune platelet refractoriness by assessing platelet recovery soon after infusion (ie, a 10- to 60-minute postinfusion platelet increment). In immune refractory states secondary to serologic incompatibility, there is poor recovery in the early postinfusion interval. In nonimmune mechanisms (ie, splenomegaly, sepsis, fever, intravascular devices, and DIC) platelet recovery within 1 hour of infusion may be adequate while longer-term survival (ie, 24-hour survival) is reduced. Serologic tests may confirm the presence of alloimmunization. Serologic tests (HLA typing or a platelet crossmatch) may also be helpful in selecting platelets with acceptable survival.

3. **Red Blood Cell Alloimmunization:** Immunization to red cell antigens may occur because of the presence of residual red cells in Platelets. Red cell compatibility testing is necessary only if the component is prepared by a method that allows the component to contain 2 mL or more of red cells, making the unit appear pink to salmon in color. When platelet components from Rh-positive donors must be given to Rh-negative females of childbearing potential because of lack of availability of Rh-negative platelets, prevention of D immunization by use of Rh Immune Globulin should be considered.
4. **Hemolysis:** Platelet transfusions that are not ABO identical may contain incompatible plasma and may cause a positive DAT and possibly, hemolysis. Platelet transfusions from group O donors with high-titer isohemagglutinins (anti-A or anti-B) may cause acute hemolytic reactions in susceptible patients.

Components Available

1. **PLATELETS (PLATELETS)** are a concentrate of platelets separated from a single unit of Whole Blood. One unit of Platelets should contain no fewer than 5.5×10^{10} platelets suspended in 40 to 70 mL of plasma. This component is usually provided as a pool. See below.
2. **POOLED PLATELETS (PLATELETS POOLED)** are composed of individual platelet units combined by aseptic technique and have an allowable shelf life as specified in the directions for use for the blood collection, processing, and storage system. The number of units of Platelets in the pool will be indicated on the label. To determine the minimum potency of this component, assume 5.5×10^{10} platelets per unit of Platelets indicated on the label. See the label for the approximate volume.
3. **PLATELETS LEUKOCYTES REDUCED (PLATELETS LEUKOCYTES REDUCED)** may be prepared using an open or closed system. One unit of Platelets Leukocytes Reduced should contain 5.5×10^{10} platelets and $<8.3 \times 10^{5}$ leukocytes. Components prepared using an open system will expire 4 hours after preparation. Components prepared using a closed system will have a shelf life as specified in the directions for use for the blood collection, processing, and storage system. This component is usually provided as a pool. See below.
4. **POOLED PLATELETS LEUKOCYTES REDUCED (PLATELETS LEUKOCYTES REDUCED, POOLED)** may be prepared by pooling and filtering Platelets or pooling Platelets Leukocytes Reduced in an open system that will have a 4-hour shelf life. The number of units in the pool will be indicated on the label. To determine the minimum potency of this component, assume 5.5×10^{10} platelets per unit of Platelets Leukocytes Reduced indicated on the label and $<5 \times 10^{6}$ leukocytes in the pool. See the label for the approximate volume. This component can also be prepared and pooled using an FDA-cleared system to provide a product with a 5-day shelf life. Components prepared using this system provide a therapeutic adult dose of platelets and $<5.0 \times 10^{6}$ leukocytes.

5. **APHERESIS PLATELETS (PLATELETS PHERESIS)** are an effective way to harvest a therapeutic adult dose of platelets from a single donor. Apheresis Platelets should contain $\geq 3.0 \times 10^{11}$ platelets. One unit of Apheresis Platelets may replace 4 to 6 units of Platelets. The volume of plasma is indicated on the label and varies between 100 and 500 mL. The number of leukocytes contained in this component varies depending upon the blood cell separator and protocol used for collection. Apheresis Platelets are supplied in one bag or in two connected bags to improve platelet viability during storage by providing more surface area for gas exchange. ACD-A is the anticoagulant solution currently used for the collection and preservation of Apheresis Platelets.
6. **APHERESIS PLATELETS LEUKOCYTES REDUCED (PLATELETS PHERESIS LEUKOCYTES REDUCED)** can be leukocyte reduced during the collection process or may be prepared by further processing using leukocyte reduction filters. Apheresis Platelets Leukocytes Reduced should contain $\geq 3.0 \times 10^{11}$ platelets and $< 5.0 \times 10^{6}$ leukocytes. When Apheresis Platelets Leukocytes Reduced are prepared by further processing, these may be labeled Apheresis Platelets Leukocytes Reduced provided the requirement for residual leukocyte count is met and the platelet recovery is at least 85% of the prefiltration content. The volume, anticoagulant-preservative, and storage conditions for Apheresis Platelets Leukocytes Reduced are the same as those for Apheresis Platelets. Apheresis Platelets Leukocytes Reduced have a shelf life of 5 days, unless the facility is participating in a post-marketing program, which allows a 7-day expiration date.

Granulocyte Components

Description

APHERESIS GRANULOCYTES Ω (GRANULOCYTES PHERESIS) contain numerous leukocytes and platelets as well as 20 to 50 mL of red cells. The number of granulocytes in each concentrate is usually $> 1.0 \times 10^{10}$. Various modalities may be used to improve granulocyte harvest, including donor administration of granulocyte colony-stimulating factor and/or corticosteroids. The final volume of the product is 200 to 300 mL including anticoagulant and plasma as indicated on the label.

Red cell sedimenting agents approved by the FDA, such as hydroxyethyl starch (HES), are typically used in the collection of granulocytes. Residual agents will be present in the final component and are described on the label. Apheresis Granulocytes should be administered as soon after collection as possible because of well-documented deterioration of granulocyte function during short-term storage. If stored, maintain at 20 to 24 C without agitation for no more than 24 hours.

Actions

Granulocytes migrate toward, phagocytize, and kill bacteria and fungi. A quantitative relationship exists between the level of circulating granulocytes and the prevalence of bacterial and fungal infection in neutropenic patients. The ultimate goal is to provide the patient with the ability to fight infection. The infusion of a granulocyte component may not be associated with a significant increase in the patient's granulocyte count and is dependent on multiple factors, including the patient's clinical condition.

Indications

Granulocyte transfusion therapy is controversial. Apheresis Granulocytes are typically used in the treatment of patients with documented infections (especially gram-negative bacteria and

fungi) unresponsive to antimicrobial therapy in the setting of neutropenia [absolute granulocyte count $<0.5 \times 10^9$/L (500/μL)] with expected eventual marrow recovery, or neonatal sepsis. A trial of broad-spectrum antimicrobial agents should be used before granulocyte transfusion therapy is initiated. If the intended recipient is CMV-seronegative and severely immunosuppressed (eg, a marrow transplant recipient), serious consideration should be given before administration of CMV-seropositive granulocytes. In addition to neutropenic patients, patients with hereditary neutrophil function defects (such as chronic granulomatous disease) may be candidates for granulocyte transfusion therapy.

Contraindications

Prophylactic use of granulocytes in noninfected patients is not routinely recommended.

Dosage and Administration

Transfuse as soon as possible. A standard blood infusion set is to be used for the administration of Apheresis Granulocytes. Do not administer using leukocyte reduction filters. Depth-type microaggregate filters and leukocyte reduction filters remove granulocytes.

The red cells in Apheresis Granulocytes must be ABO compatible. Once granulocyte transfusion therapy is initiated, support should continue at least daily until infection is cured, defervescence occurs, the absolute granulocyte count returns to at least 0.5×10^9/L (500/μL), or the physician in charge decides to halt the therapy.

Because most patients receiving these products are severely immunosuppressed, Apheresis Granulocytes are usually irradiated to prevent TA-GVHD (see section on Further Processing).

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the section on Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are hazards that apply specifically to Apheresis Granulocytes.

1. **Febrile Nonhemolytic Reactions:** These reactions are frequently noted in patients receiving granulocyte transfusions. Fever and chills in patients receiving granulocyte components may be avoided or mitigated by slow administration and recipient premedication.
2. **Allergic Reactions:** Allergic reactions to HES and other red cell sedimenting solutions may occur during granulocyte transfusion.
3. **Pulmonary Reactions:** Granulocyte transfusion can cause worsening of pulmonary function in patients with pneumonia, and rarely severe pulmonary reactions, especially in patients receiving concomitant amphotericin B.
4. **Alloimmunization:** Immunization to HLA antigens frequently occurs with granulocyte transfusion and can cause refractoriness to platelet transfusion.

Further Processing

This section addresses further processing of previously described blood components. The processes described in this section are: Leukocyte reduction, identification of CMV-seronegative components, irradiation, and washing. A component may undergo one or more of these processes.

Leukocyte Reduction

Description

A unit of whole blood generally contains ≥1 to 10×10^9 white cells. Leukocyte reduction may be achieved by in-process collection or filtration: 1) soon after collection (prestorage), 2) after varying periods of storage in the laboratory, or 3) at the bedside. The method used in the laboratory for leukocyte reduction is subject to quality control testing; leukocyte-reduced components prepared at the bedside are not routinely subjected to quality control testing. Leukocyte reduction will decrease the cellular content and volume of blood according to characteristics of the filter system used. Red Blood Cells Leukocytes Reduced, Apheresis Red Blood Cells Leukocytes Reduced, and Apheresis Platelets Leukocytes Reduced must have a residual content of leukocytes $<5.0 \times 10^6$ and Platelets Leukocytes Reduced must have $<8.3 \times 10^5$ residual leukocytes. Leukocyte reduction filters variably remove other cellular elements in addition to white cells. Washing is not a substitute for leukocyte reduction. Leukocyte reduction is not a substitute for irradiation.

Indications

Leukocyte-reduced components are indicated to decrease the frequency of recurrent febrile nonhemolytic transfusion reactions. They have also been shown to reduce the risk of transfusion-transmitted CMV and to reduce the incidence of HLA alloimmunization.

Contraindications

Leukocyte-reduced components do not prevent TA-GVHD. Leukocyte reduction filters are not to be used in the administration of Apheresis Granulocytes or Apheresis Granulocytes/Platelets.

Side Effects and Hazards

The use of blood components that are leukocyte reduced at the bedside may cause unexpected severe hypotension in some recipients, particularly those taking angiotensin converting enzyme inhibitor medication.

Specific Leukocyte-Reduced Components

RED BLOOD CELLS LEUKOCYTES REDUCED (RED BLOOD CELLS LEUKOCYTES REDUCED)
APHERESIS RED BLOOD CELLS LEUKOCYTES REDUCED (RED BLOOD CELLS PHERESIS LEUKOCYTES REDUCED)
PLATELETS LEUKOCYTES REDUCED (PLATELETS LEUKOCYTES REDUCED)
APHERESIS PLATELETS LEUKOCYTES REDUCED (PLATELETS PHERESIS LEUKOCYTES REDUCED)

Further Testing to Identify CMV-Seronegative Blood

Description

CMV-seronegative blood is selected by performing testing for antibodies to CMV. Transmission of CMV disease is associated with cellular blood components. Plasma, cryoprecipitate, and other plasma-derived blood components do not transmit CMV; therefore, CMV testing is not required for these components.

Indications

Transfusion of CMV-negative blood is indicated in CMV-seronegative recipients who are at risk for severe CMV infections. These at-risk groups include pregnant women and their fetuses, low

birthweight infants, hematopoietic progenitor cell transplant recipients, solid-organ transplant recipients, severely immunosuppressed recipients, and HIV-infected patients. Leukocyte-reduced components may be an alternative to CMV-seronegative transfusion in some clinical conditions.

Irradiation

Description

Blood components that contain viable lymphocytes may be irradiated to prevent proliferation of T lymphocytes, which is the immediate cause of TA-GVHD. Irradiated blood is prepared by exposing the component to a radiation source. The standard dose of gamma irradiation is 2500 cGy targeted to the central portion of the container with a minimum dose of 1500 cGy delivered to any part of the component.

Indications

Irradiated cellular components are indicated for use in patient groups that are at risk for TA-GVHD from transfusion. At-risk groups include: fetal and neonatal recipients of intrauterine transfusions, selected immunocompromised recipients, recipients of cellular components known to be from a blood relative, recipients who have undergone marrow or peripheral blood progenitor cell transplantation, and recipients of cellular components whose donor is selected for HLA compatibility.

Side Effects and Hazards

Irradiation induces erythrocyte membrane damage. Irradiated red cells have been shown to have higher supernatant potassium levels than nonirradiated red cells. Removal of residual supernatant plasma before transfusion may reduce the risks associated with elevated plasma potassium. The expiration date of irradiated red cells is changed to 28 days after irradiation if remaining shelf life exceeds 28 days. There are no known adverse effects following irradiation of platelets; the expiration date is unchanged.

Washing

Description

Washed components are typically prepared using 0.9% Sodium Chloride, Injection (USP) with or without small amounts of dextrose. Washing removes unwanted plasma proteins, including antibodies and glycerol from previously frozen units. There will also be some loss of red cells and platelets, as well as a loss of platelet function through platelet activation. The shelf life of washed components is no more than 24 hours at 1 to 6 C or 4 hours at 20 to 24 C. Washing is not a substitute for leukocyte reduction.

Indications

Washing of blood components is indicated to remove unwanted plasma when it contains constituents that predispose patients to significant transfusion reactions (eg, the removal of IgA-containing plasma in providing transfusion support for an IgA-deficient recipient or in rare recipients experiencing anaphylactoid reactions to plasma components).

Specific Washed Components

WASHED RED BLOOD CELLS (RED BLOOD CELLS WASHED)
WASHED APHERESIS RED BLOOD CELLS (RED BLOOD CELLS PHERESIS WASHED)
WASHED PLATELETS (PLATELETS WASHED)
WASHED APHERESIS PLATELETS (PLATELETS PHERESIS WASHED)

Volume Reduction

Description

Volume reduction is a special manipulation of cellular blood products using centrifugation. The process involves the aseptic removal of a portion of the supernatant, containing plasma and storage medium. Volume reduction removes excess plasma, thereby reducing unwanted plasma proteins, including antibodies. It is more commonly used in pediatric and in-utero transfusions. There will be some loss of platelet function through platelet activation as a result of volume reduction. The shelf life of volume-reduced components is no more than 24 hours at 1 to 6 C or 4 hours at 20 to 24 C.

Indications

Reducing the plasma volume of cellular components is indicated in cases where the volume status of a patient is being aggressively managed, such as in infants with compromised cardiac function. Volume reduction may be used to reduce exposure to plasma proteins or additives (such as mannitol), to achieve a specific component concentration, or to reduce exposure to antibodies targeting known recipient antigens (especially in an Apheresis Platelet unit containing ABO-incompatible plasma collected from a mother for the treatment of neonatal alloimmune thrombocytopenia).

Contraindications

Volume reduction is not a substitute for washing or for dosing with small aliquots.

Volume reduction of platelets may result in adverse consequences associated with overtransfusion of platelets.

Specific Volume-Reduced Components

RED BLOOD CELLS VOLUME REDUCED (VOLUME REDUCED RED BLOOD CELLS)
APHERESIS RED BLOOD CELLS VOLUME REDUCED (VOLUME REDUCED RED BLOOD CELLS PHERESIS)
PLATELETS VOLUME REDUCED (VOLUME REDUCED PLATELETS)
APHERESIS PLATELETS VOLUME REDUCED (VOLUME REDUCED PLATELETS PHERESIS)

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Table 4. Summary Chart of Blood Components

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Red Blood Cells; Red Blood Cells, Low Volume; Apheresis Red Blood Cells	Symptomatic anemia.	Increases oxygen-carrying capacity.	Pharmacologically treatable anemia. Coagulation deficiency. Volume expansion.	Must be ABO compatible.	Infectious diseases. Hemolytic, septic/toxic, allergic, febrile reactions. TACO. TRALI. TA-GVHD.	As fast as patient can tolerate but less than 4 hours.
Deglycerolized Red Blood Cells	See Red Blood Cells. IgA deficiency with anaphylactoid reaction.	See Red Blood Cells. Deglycerolization removes plasma proteins. Risk of allergic and febrile reactions reduced.	See Red Blood Cells.	See Red Blood Cells.	See Red Blood Cells. Hemolysis due to incomplete deglycerolization can occur.	See Red Blood Cells.
Red Blood Cells Leukocytes Reduced; Apheresis Red Blood Cells Leukocytes Reduced	See Red Blood Cells. Reduction of febrile reactions.	See Red Blood Cells Reduction of leukocytes reduces risk of febrile reactions, HLA alloimmunization and CMV infection.	See Red Blood Cells. Leukocyte reduction should not be used to prevent TA-GVHD.	See Red Blood Cells.	See Red Blood Cells. Hypotensive reaction may occur if bedside leukocyte reduction filter is used.	See Red Blood Cells.
Washed Red Blood Cells	See Red Blood Cells. IgA deficiency with anaphylatoid reaction. Recurrent severe allergic reactions to unwashed red cell products.	See Red Blood Cells. Washing reduces plasma proteins. Risk of allergic reactions may be reduced.	See Red Blood Cells.	See Red Blood Cells.	See Red Blood Cells.	See Red Blood Cells.

(Continued)

Table 4. Summary Chart of Blood Components (Continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Whole Blood	Symptomatic anemia with large volume deficit.	Increases oxygen-carrying capacity. Increases blood volume.	Condition responsive to specific component. Treatment of coagulopathy.	Must be ABO identical.	See Red Blood Cells.	As fast as patient can tolerate but less than 4 hours.
Fresh Frozen Plasma (FFP)	Clinically significant plasma protein deficiencies when no specific coagulation factors are available. TTP.	Source of plasma proteins, including all coagulation factors.	Volume expansion. Coagulopathy that can be more effectively treated with specific therapy.	Must be ABO compatible.	Infectious diseases. Allergic reactions. TACO. TRALI.	Less than 4 hours.
Plasma Frozen Within 24 Hours After Phlebotomy (PF24)	Clinically significant deficiency of stable coagulation factors.	Source of nonlabile plasma proteins. Levels of Factor VIII are significantly reduced and levels of Factor V and other labile plasma proteins are variable compared with FFP.	Volume expansion. Deficiencies of labile coagulation factors including Factors VIII and V.	Must be ABO compatible.	See FFP.	Less than 4 hours.
Plasma Cryoprecipitate Reduced	TTP.	Plasma protein replacement for plasma exchange in TTP. Deficient in fibrinogen, Factor VIII, vWF, and Factor XIII. Deficient in high-molecular-weight vWF multimers as compared to FFP.	Volume expansion. Deficiency of coagulation factors known to be depleted in this product, fibrinogen, Factors VIII, vWF, and XIII.	Must be ABO compatible.	See FFP.	Less than 4 hours.

(Continued)

Table 4. Summary Chart of Blood Components (Continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Thawed Plasma Ω	Bleeding patients except consumptive coagulopathy.	Source of plasma proteins.	Not indicated as treatment for isolated coagulation factor deficiencies.	Must be ABO compatible.	See FFP.	Less than 4 hours.
	Reversal of warfarin effect.	Levels and activation state of coagulation proteins in thawed plasma are variable and change over time.	Levels and activation state of coagulation proteins in thawed plasma are variable and change over time.			
Liquid Plasma	Initial treatment of patients undergoing massive transfusion.	Coagulation support for life-threatening trauma/ hemorrhages.	Not indicated as treatment for isolated coagulation factor deficiencies.	Must be ABO compatible.	See FFP.	Less than 4 hours.
		The profile of plasma proteins in Liquid Plasma is poorly characterized. Levels and activation state of coagulation proteins are dependent upon and change with time in contact with cells, as well as the conditions and duration of storage.	The profile of plasma proteins in Liquid Plasma is poorly characterized. Levels and activation state of coagulation proteins are dependent upon and change with time in contact with cells, as well as the conditions and duration of storage.			

(Continued)

Table 4. Summary Chart of Blood Components (Continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Cryoprecipitated AHF; Pooled Cryoprecipitated AHF	Hypofibrinogenemia. Factor XIII deficiency. von Willebrand disease. Hemophilia A.	Provides fibrinogen, vWF, Factor XIII, and Factor VIII.	Deficiency of any plasma protein other than those enriched in Cryoprecipitated AHF.		Infectious diseases. Allergic reactions.	Less than 4 hours.
Platelets; Pooled Platelets	Bleeding due to thrombocytopenia or platelet function abnormality. Prevention of bleeding from marrow hypoplasia.	Improves hemostasis.	Plasma coagulation deficits. Some conditions with rapid platelet destruction (eg, ITP, TTP) unless life-threatening hemorrhage.	Should not use some filters (check manufacturer's instructions).	Infectious diseases. Septic/toxic, allergic, febrile reactions. TACO. TRALI. TA-GVHD.	Less than 4 hours.
Apheresis Platelets	See Platelets.	See Platelets. May be HLA (or other antigen) selected.	See Platelets.	See Platelets.	See Platelets.	See Platelets.
Platelets Leukocytes Reduced; Pooled Platelets Leukocytes Reduced; Apheresis Platelets Leukocytes Reduced	See Platelets. Reduction of febrile reactions. Reduction of HLA alloimmunization.	See Platelets. Reduction of leukocytes reduces risk of febrile reactions, HLA alloimmunization, and CMV infection.	See Platelets. Leukocyte reduction should not be used to prevent TA-GVHD.	See Platelets.	See Platelets.	See Platelets.
Apheresis Granulocytes Ω ; Apheresis Granulocytes/ Platelets Ω	See Platelets. Neutropenia with infection, unresponsive to appropriate antibiotics.	Provides granulocytes with or without platelets.	Infection responsive to antibiotics, eventual marrow recovery not expected.	Must be ABO compatible. Should not use some filters (check manufacturer's instructions).	Infectious diseases. Hemolytic, allergic, febrile reactions. TACO. TRALI. TA-GVHD.	One unit over 2-4 hours. Closely observe for reactions.

(Continued)

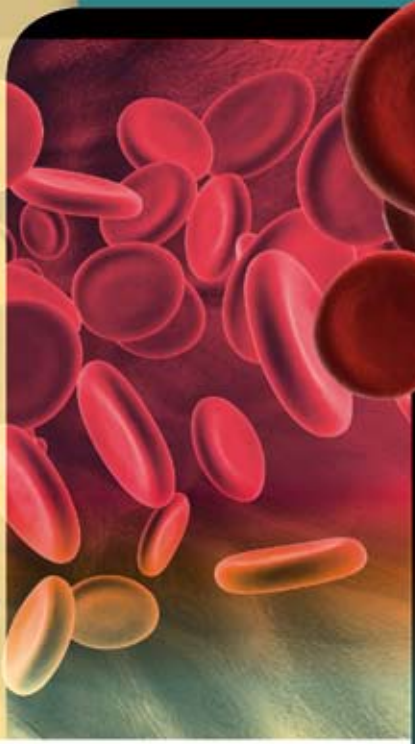
Table 4. Summary Chart of Blood Components (Continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Further Processing:						
Irradiated Components	See component. Increased risk for TA-GVHD (eg, congenital immunodeficiencies, HLA-matched platelets or transfusions from blood relatives).	Donor lymphocytes are inactivated reducing risk of TA-GVHD.	See component.	See component.	See component.	See component.

*For all cellular components there is a risk the recipient may become alloimmunized and experience rapid destruction of certain types of blood products. Red-cell-containing components and thawed plasma (thawed FFP, thawed PF24, or Thawed Plasma) should be stored at 1-6 C. Platelets, Granulocytes, and thawed Cryoprecipitate should be stored at 20-24 C. Disclaimer: Please check the corresponding section of the *Circular* for more detailed information.

TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury; TA-GVHD = transfusion-associated graft-vs-host disease; CMV = cytomegalovirus; TTP = thrombotic thrombocytopenic purpura; AHF = antihemophilic factor; ITP = immune thrombocytopenic purpura; vWF = von Willebrand factor.

Practice Guidelines for Blood Transfusion



A Compilation from Recent Peer-Reviewed Literature

Second Edition

Ame i

First Edition, May 2002

Authors:
Ritchard Cable, M.D., Connecticut Region
Brian Carlson, M.D., Tennessee Valley Region
Linda Chambers, M.D., Biomedical Headquarters
Jerry Kolins, M.D., Southern California Region
Scott Murphy, M.D., Penn-Jersey Region
Lowell Tilzer, M.D., Central Plains Region
Ralph Vassallo, M.D., Penn-Jersey/NE Pennsylvania Regions
John Weiss, M.D., Badger-Hawkeye Region
Mary Ellen Wissel, M.D., Central Ohio Region

Second Edition, April 2007

Revised by:
Yvette Miller, M.D. (Chair), Arizona Region
Gary Bachowski, M.D., Ph.D., North Central Region
Richard Benjamin, M.D., Ph.D., Biomedical Headquarters
Diane K. Eklund, M.D., Northern California Region
A.J. Hibbard, M.D., Badger-Hawkeye Region
Thomas Lightfoot, M.D., New York-Penn Region
Claire Meena-Leist, M.D., Indiana-Ohio Region
NurJehan Quraishy, M.D., Western Lake Erie Region
Suneeti Sapatnekar, M.D., Ph.D., Northern Ohio Region
Jerry Squires, M.D., Ph.D., Biomedical Headquarters
Annie Strupp, M.D., Lewis and Clark Region
Ralph Vassallo, M.D., Penn-Jersey Region
John Weiss, M.D., Ph.D., Badger-Hawkeye Region

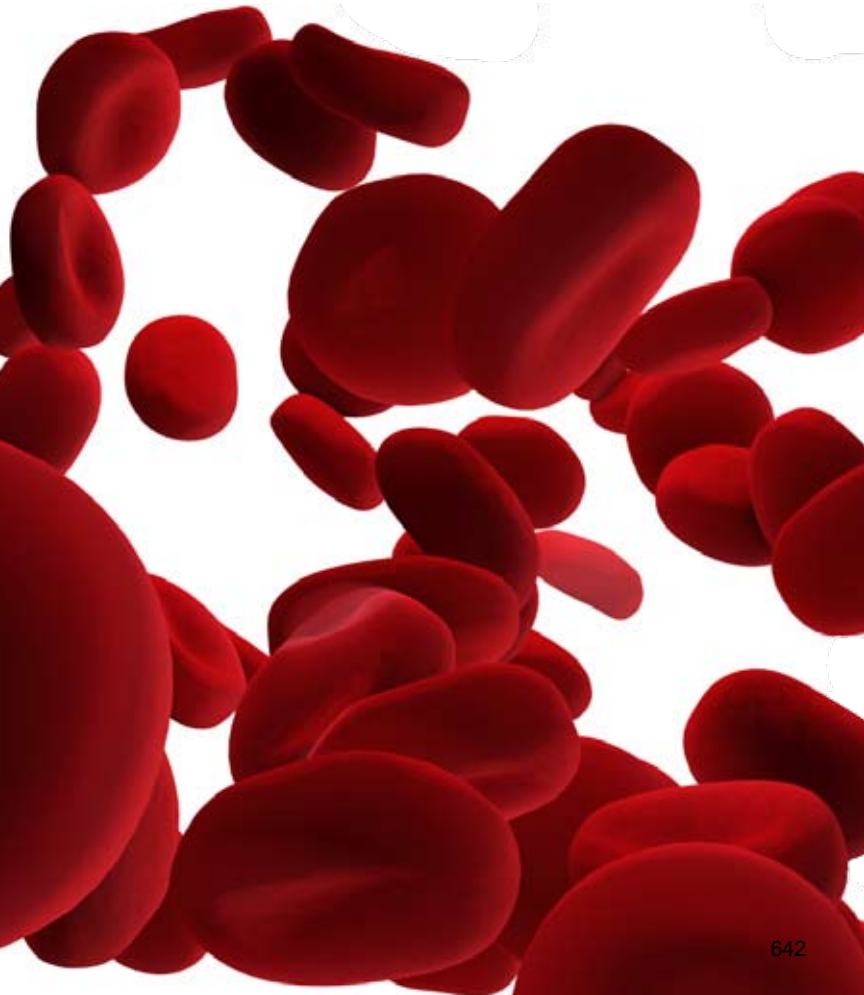
Graphic Designer: George Ramirez

Practice Guidelines for Blood Transfusion:

A Compilation from Recent Peer-Reviewed Literature

Second Edition

Users of this brochure should refer to the Circular of Information regarding the approved indications, contraindications and risks of transfusion, and for additional descriptions of blood components. Copies of the Circular of Information can be obtained from your American Red Cross region or through the AABB (internet address http://www.aabb.org). The complete text of the side effects and hazards of blood transfusion from the current Circular of Information appears in an appendix at the end of this brochure.



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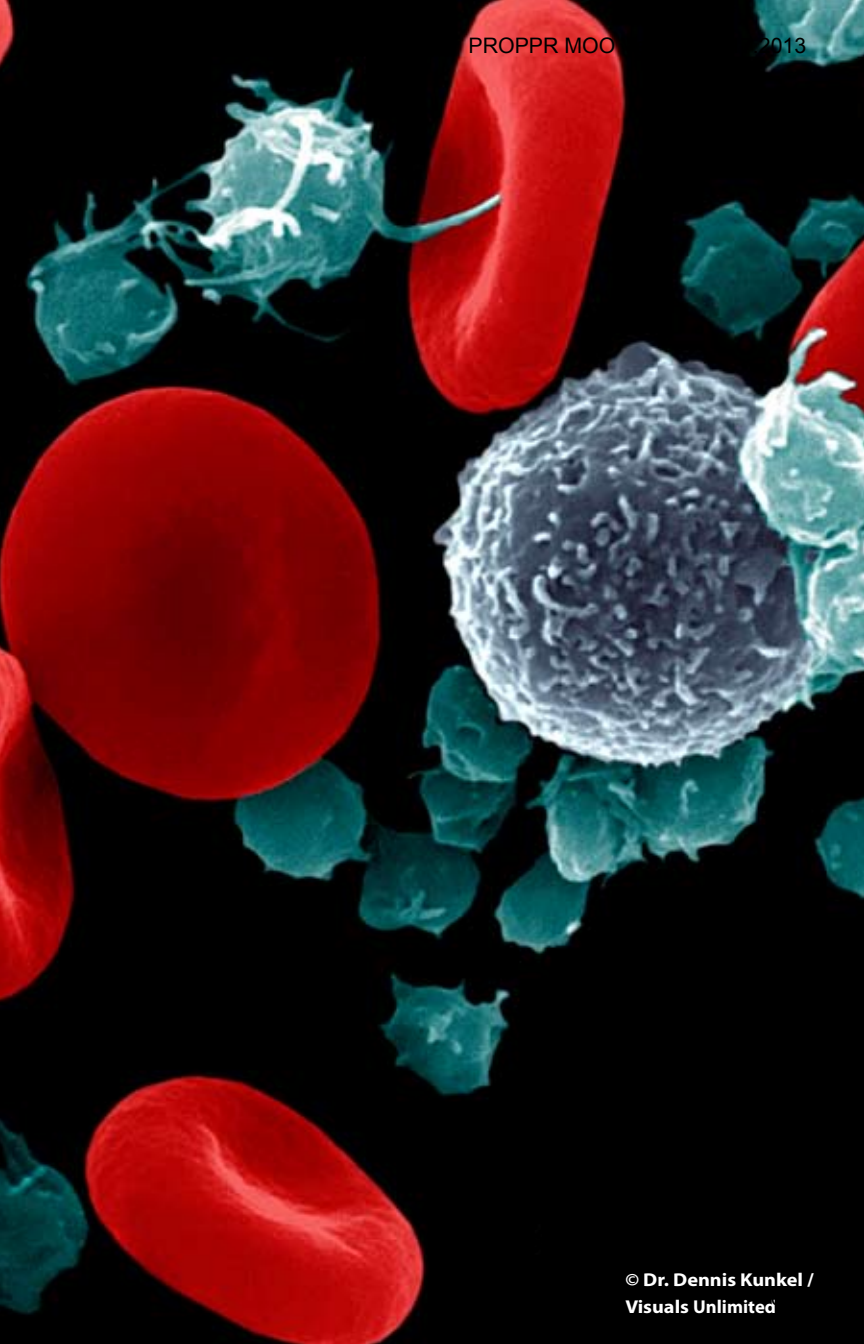
INTRODUCTION

Accrediting and regulatory agencies make specific mention of blood transfusion in a number of core functions essential to quality medical care. For example, the need for transfusion is considered one of the key parameters for determining the appropriateness of an operative procedure. An acute hemolytic transfusion reaction due to ABO incompatibility is specifically identified as a reviewable sentinel event for which a comprehensive analysis of cause, corrective action, preventive action and reporting are required. Blood transfusion is acknowledged to be a therapy that involves risks, so that the organization's performance monitoring and improvement program must address the use of blood and blood components. Furthermore, a cross functional group of medical and support staff is charged with the responsibility to take the leadership role in improving transfusion practice when indicated.

Successful performance of these functions requires that the medical staff agree to some set of practice guidelines for ordering blood transfusion. Ideally, practice guidelines would be grounded in well-designed clinical trials that clearly establish efficacy and quantify risk, in at least the most common settings in which this therapy is applied. The current literature does provide guidelines for some of the more commonly encountered clinical situations. However, variability in transfusion practice often reflects expert opinion, tradition, community practice, or personal experience.

Given the known and hypothetical risks of transfusion, as well as the cost, liability and workload involved with this therapy, there are many reasons to move the basis of transfusion practice in a particular institution away from anecdotal experience and tradition, and toward expert advice and clinical evidence. This brochure was revised in order to provide up to date blood usage guidelines from experts and expert panels, as well as the results of significant clinical transfusion trials, published in the English language in peer-reviewed journals since 2002. The authors, all of whom are physician staff for the American Red Cross, have made every attempt to fairly reproduce the advice and lessons contained in these publications. It is their hope that this brochure will be a valuable resource to hospitals who obtain blood and blood components from the American Red Cross as they develop and update their blood usage guidelines for the purpose of improving transfusion safety.



RED BLOOD CELLS | GENERAL INFORMATION

Components:

Approved name: Red Blood Cells.

Also referred to as Packed Cells, Red Cells, Packed Red Blood Cells, RBCs.

Preparation variations include Red Blood Cells (Adenine-Saline Added); Red Blood Cells Leukocytes Reduced (LR-RBC); Red Blood Cells Apheresis; Red Blood Cells Deglycerolized; Red Blood Cells Irradiated; Red Blood Cells, Low Volume; and Red Blood Cells Washed. Whole blood is rarely required and is therefore not addressed.

Description of Components:

Red Blood Cells consist of erythrocytes concentrated from whole blood donations by centrifugation or collected by apheresis method. The component is anticoagulated with citrate and may have had one or more preservative solutions added.

Depending on the preservative-anticoagulant system used, the hematocrit of Red Blood Cells ranges from about 50-65% (e.g., AS-1, AS-3, AS-5) to about 65-80% (e.g., CPDA-1, CPD, CP2D). Red Blood cells contain an average of about 50 mL of donor plasma (range 20 mL to 150 mL), in addition to the added preservative and anticoagulant solutions.

Each unit contains approximately 42.5-80 g of hemoglobin or 128-240 mL of pure red cells, depending on the hemoglobin level of the donor, the starting whole blood collection volume, and the collection methodology or further processing. When leukoreduced, RBC units must retain at least 85% of the red cells in the original component.

Each unit of Red Blood Cells contains approximately 147-278 mg of iron, most in the form of hemoglobin.

Ref. 6, 15

Selection and Preparation:

Red Blood Cells must be compatible with ABO antibodies present in the recipient serum, and crossmatched (serologic or electronic) to confirm compatibility with ABO and other antibodies prior to routine transfusion.

Extended storage preservative-anticoagulant preparations such as AS-1 and AS-3 are appropriate for nearly all patient types. Physicians concerned about preservative-anticoagulant in neonates may elect to use a different preparation (e.g., CPD or CPDA-1) or to remove preservative-anticoagulant from transfusion aliquots prior to administration, for example, by centrifugation and volume reduction or washing.

Red Blood Cells are capable of transmitting cytomegalovirus, mediating graft-versus-host disease and causing febrile, nonhemolytic reactions. For recipients at particular risk from these transfusion-related complications, use of CMV reduced-risk (i.e. CMV seronegative or LR-RBC), gamma-irradiated and leukoreduced preparations should be considered.

Dosing:

A dose of one unit of compatible Red Blood Cells will increase the hemoglobin level in an average sized adult who is not bleeding or hemolyzing by approximately 1 g/dL or Hct by 3%. In neonates, a dose of 10-15 mL/kg is generally given, and AS-1 or AS-3 packed red cells with a hematocrit of approximately 60% will increase the hemoglobin by about 3 g/dL.

Response:

Unless the recipient is bleeding or hemolyzing, and provided the transfused red cells are compatible, the post-transfusion hemoglobin can be accurately predicted from the patient's estimated blood volume, baseline red cell volume (=blood volume X venous

hematocrit X 0.91) and transfusion volume.

Transfused red cells have a half-life of approximately 30 days in the absence of other processes that would result in red cell loss or premature removal.

Ref. 27

Indications and Contra-indications:

Red blood cells are indicated for patients with a symptomatic deficiency of oxygen-carrying capacity or tissue hypoxia due to an inadequate circulating red cell mass. They are also indicated for exchange transfusion (e.g., for hemolytic disease of the newborn) and red cell exchange (e.g., for acute chest syndrome in sickle cell disease).

Patients must be evaluated individually to determine the proper transfusion therapy, taking care to avoid inappropriate over- or under- transfusion. Transfusion decisions should be based on clinical assessment and not on laboratory values alone.

Red blood cells should not be used to treat anemia that can be corrected with a non-transfusion therapy (e.g. iron therapy). They also should not be used as a source of blood volume, or oncotic pressure or to improve wound healing, or sense of well being.

For complete Side Effects and Hazards see appendix.

Perioperative/Periprocedural:

General:

The function of a RBC transfusion is to augment oxygen delivery to tissues. Hemoglobin levels during active bleeding are imprecise measures of tissue oxygenation. Adequate or inadequate fluid resuscitation can significantly alter the measured hemoglobin concentration. In addition, a number of factors must be considered besides the blood hemoglobin level such as oxygenation in the lungs, blood flow, hemoglobin-oxygen affinity and tissue demands for oxygen.

Consequently, the adequacy of oxygen delivery must be assessed in individual patients, particularly in patients with limited cardiac reserve or significant atherosclerotic vascular disease. If available, mixed venous O_2 levels, O_2 extraction ratios, or changes in oxygen consumption may be helpful in assessing tissue oxygenation. Other factors to consider, in addition to the above, include anticipated degree and rate of blood loss and the effect of body temperature or drugs/anesthetics on oxygen consumption. Notwithstanding the above, the following recommendations are made by an American Society of Anesthesiologists Task Force:

1. Transfusion is rarely indicated when the hemoglobin level is above 10 g/dL and is almost always indicated in patients when the hemoglobin level is below 6 g/dL;

2. The determination of transfusion in patients whose hemoglobin level is 6-10 g/dL should be based on any ongoing indication of organ ischemia, the rate and magnitude of any potential or actual bleeding, the patient's intravascular volume status and risk of complications due to inadequate oxygenation.

The use of alternative measures to reduce allogeneic red cell use should be considered, including preoperative autologous donation, intra-operative and post-operative autologous blood recovery, acute normovolemic hemodilution, and operative and pharmacologic

measures that reduce blood loss.

Ref. 7

Critical Care:

General:

The same considerations regarding individualization of red cell transfusions apply to critical care as perioperative patients (see above). The effects of anemia must be separated from those of hypovolemia, although both can impede tissue oxygen delivery. Blood loss of greater than 30% of blood volume causes significant clinical symptoms but resuscitation with crystalloid alone is usually successful in young healthy patients with blood loss of up to 40% of blood volume (e.g., 2- liter blood loss in an average adult male). Beyond that level of acute blood loss after adequate volume resuscitation, acute normovolemic anemia will exist. However, oxygen delivery in healthy adults is maintained even with hemoglobin levels as low as 6-7 g/dL. Thus up to 40% of the blood volume in a bleeding, otherwise healthy young adult can be replaced with crystalloid without the need for red cell transfusion.

In support of a conservative red cell transfusion policy in critical care is a multicenter, randomized, controlled trial comparing a transfusion trigger of 7 g/dL with a trigger of 9 g/dL in normovolemic critically ill patients. Overall 30-day mortality was similar in the two groups and in the subset of more seriously ill patients. However, in less acutely ill or younger patients, the restrictive strategy resulted in lower 30-day mortality.

In support of considering cardiovascular status in the decision to transfuse red cells is a retrospective study of transfusion in elderly patients with acute myocardial infarction which showed lower short-term mortality when patients were transfused with a hemoglobin as high as 10 g/dL.

Thus, transfusion triggers for red cells in critical care

must be customized to defined patient groups, and the decision to transfuse must be made on the basis of individual patient characteristics. Unfortunately, the availability of carefully performed clinical trials to assist the clinician is extremely limited.

Ref. 24, 62

Neonates:

Neonates and Critically Ill Children:

Infants may require simple or exchange transfusions for hemolytic disease of the newborn (HDN) or symptomatic anemia in the first months of life.

The American Academy of Pediatrics has published guidance on specific indications for exchange transfusion for newborn infants 35 or more weeks of gestation with hyperbilirubinemia, including that caused by HDN. Infants with jaundice caused by HDN are at greater risk of bilirubin encephalopathy and are treated more intensively than infants with "physiologic" jaundice at any given serum unconjugated bilirubin concentration.

Ref. 3

Apart from HDN, neonatal anemia occurs in many preterm infants because of iatrogenic blood loss for laboratory tests, concurrent infection or illness and inadequate hematopoiesis in the first weeks of life. Transfusion thresholds for preterm infants and critically ill children have been widely debated for years, but recent randomized studies support the use of a restrictive strategy (e.g. transfusion at lower hemoglobin thresholds) compared to more liberal criteria (e.g. transfusion at higher hemoglobin thresholds).

In the multicenter PINT (Premature Infants in Need of Transfusion) study, 451 very low birthweight infants were randomly assigned to receive red cell transfusions either by restrictive or liberal criteria. Infants in the restrictive transfusion group had lower mean hemoglobin values than infants in the liberal group, and more infants

avoided transfusion completely in the restrictive group (5%) compared to the liberal group (11%). There was no difference between the two groups in the composite outcome (death, severe retinopathy, bronchopulmonary dysplasia, and brain injury), supporting the use of restrictive transfusion criteria. In a smaller, single-center trial, Bell et al. randomized 100 preterm infants to either restrictive or liberal transfusion criteria, and found a reduction in the number of transfusions in the restrictive group. However, infants in the restrictive group were noted to have more apnea episodes and neurologic events than infants in the liberal group. In conclusion, the documented benefits of restrictive transfusion practice are a decrease in the number of transfusions and exposure to fewer RBC donors, if a limited-donor program is not used. It is possible that the higher hemoglobin values maintained in the liberal transfusion group in the study of Bell et al. compared with the corresponding group in the PINT trial may have decreased the risk of apnea and brain injury.

These two randomized studies suggest that transfusion thresholds can be lower than what are currently followed in most hospitals, but identify the need for additional clinical studies. General guidelines for transfusion must take into consideration the infants' cardiorespiratory status but transfusion decisions must be tailored to the individual patient.

Table: General Guidelines For Small-volume (10-15 mL/kg) Transfusion To Infants:

Maintain HCT between :	Clinical Status
40-45%	Severe cardiopulmonary disease* (e.g., mechanical ventilation >0.35 FiO_2)
30-35%	Moderate cardiopulmonary disease (e.g. less intensive assisted ventilation such as nasal CPAP or supplemental oxygen)
30-35%	Major surgery
20-30%	Stable anemia, especially if unexplained breathing disorder or unexplained poor growth

*Must be defined by institution

Strauss R., ISBT Science Series 2006, 1:11-4, Blackwell Publishing Ltd., reprinted with permission.

Ref. 11, 12, 26, 57

Less controversial are the results from the TRIPICU (Transfusion Requirements in the Pediatric Intensive Care Unit) study, which demonstrated a hemoglobin threshold of 7 g/dL for red-cell blood transfusion is not inferior to a treatment strategy using a hemoglobin threshold of 9.5 g/dL among critically ill but stable children being treated in ICUs. A higher threshold may be indicated for patients with cardiovascular disease or children with severe hypoxemia, hemodynamic instability, active blood loss or cyanotic heart disease.

Ref. 17, 28, 57

Hematology/Oncology:

Asymptomatic Chronic Anemia:
Treat with pharmacologic agents based on the specific diagnosis (e.g., Vit B12, folic acid, recombinant erythropoietin, iron).

Symptomatic Chronic Anemia:
Transfuse to minimize symptoms and risks associated with anemia. Transfusion is usually required when hemoglobin is at 6 g/dL.

Severe Thalassemia:
Transfuse to help prevent symptomatic anemia and suppress endogenous erythropoiesis by maintaining hemoglobin at 9.5-10.5 g/dL.

Sickle Cell Disease:
Evidence-based clinical guidelines and consensus statements have outlined indications for transfusion in sickle cell disease. SCD patients should be transfused with leukocyte-poor, antigen-matched blood to reduce the frequency of transfusion reactions and the development of antibodies. The choice between simple transfusion as opposed to exchange transfusion is often based on clinical judgment and available resources, with few clinical studies to guide decisions. In preparation for surgery requiring general anesthesia, however, simple transfusion to increase hemoglobin to 10 g/dL was as effective as exchange transfusion in preventing perioperative complications in patients with sickle cell anemia and was associated with less blood usage and a lower rate of red cell alloimmunization.

Chronic transfusion therapy to maintain the HbS below 30% of the total hemoglobin prevents first stroke in high-risk children with abnormal transcranial Doppler studies and prevents recurrent stroke in those with a history of infarctive stroke. The treatment goal for prevention of recurrent stroke may be relaxed to less than 50% HbS after several complication-free years, but treatment

cannot be safely discontinued at any point. Similarly, prophylactic transfusion cannot be safely discontinued in children with sickle cell anemia who have abnormalities on transcranial Doppler studies at high risk of stroke (STOP 2). In contrast to simple transfusion, exchange transfusion can prevent iron accumulation and may reverse iron overload in chronically transfused patients.

Accepted Indications for Transfusion in Sickle Cell Disease:

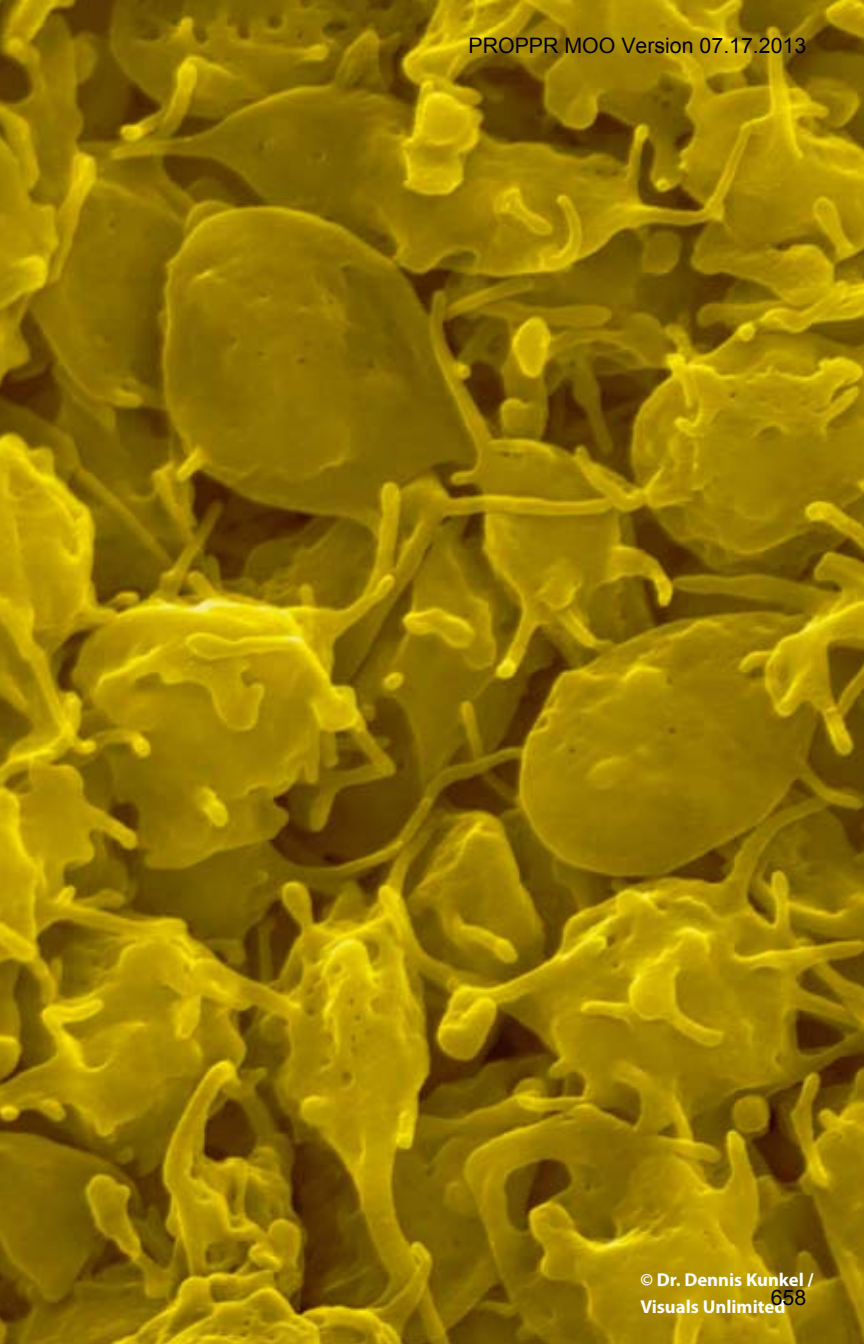
Episodic or Acute Complications of SCD	Chronic Complications of SCD
• Severe anemia	• Prevention of stroke in children with abnormal transcranial Doppler studies*
• Acute splenic sequestration	• Prevention of stroke recurrence*
• Transient red cell aplasia	• Chronic debilitating pain
• Preparation for general anesthesia	• Pulmonary hypertension
• Sudden severe illness*	• Anemia associated with chronic renal failure
• Acute chest syndrome*	
• Stroke*	
• Acute multiorgan failure*	

*Managed with simple transfusion or erythrocytapheresis

Ref. 2, 25, 30, 34, 59, 60

Controversial indications:
Priapism
Leg ulcers
Pregnancy
Preparation for infusion of contrast media
"Silent" cerebral infarct and/or neurocognitive damage

Inappropriate Indications and Contraindications:
- Chronic, steady-state (asymptomatic anemia)
- Uncomplicated pain episodes
- Infection
- Minor surgery that does not require general anesthesia
- Aseptic necrosis of the hip or shoulder (unless indicated for surgery)
- Uncomplicated pregnancy



PLATELETS | GENERAL INFORMATION

Components:

Approved names: Platelets; Platelets Pooled; Platelets Pheresis.

Platelets are also referred to as whole blood derived platelets, random donor platelets, randoms, platelet concentrates, or RDPs. Platelets Pheresis are also referred to as single donor platelets, or SDPs.

Preparation variations include Platelets pre-storage pooled, Platelets Irradiated; Platelets Pooled Irradiated; Platelets Pheresis Irradiated; Platelets Leukocytes Reduced; Platelets Pheresis Leukocytes Reduced; and Platelets Pheresis, Leukocytes Reduced, Irradiated.

Description of Components:

Platelets (RDP): derived from Whole Blood; should contain $\geq 5.5 \times 10^{10}$ platelets (average content approximately 8.0×10^{10}) per bag in approximately 50 mL of plasma. Anticoagulant is the same as used for the whole blood collection, usually CPD or CP2D. Prestorage pooled platelets should contain ($\geq 5.5 \times 10^{10}$) x number of RDP in the pool.

Platelets Pheresis (SDP): obtained using automated instrumentation; should contain $\geq 3.0 \times 10^{11}$ platelets (average content approximately $3.5\text{-}4.0 \times 10^{11}$) per bag in about 250 mL of plasma. Anticoagulant is ACD.

Selections and Preparations:

Four to ten RDPs are pooled at the blood center (prestorage pooled platelets) or the hospital prior to transfusion to prepare an adult dose. SDPs are ready for transfusion.

SDPs and RDPs should be ABO-identical with the recipient when possible.

Rh-negative recipients should receive Rh-negative platelets when possible, particularly in women of childbearing potential. Consider administering Rh immune globulin if Rh-positive platelets need to be administered.

Patients at risk for transfusion-associated graft-versus host disease (TA-GVHD) should received gamma-irradiated platelets.

Dosing:

Four to ten units of pooled RDPs or one SDP for thrombocytopenia or thrombocytopathy meeting pre-specified triggers.

To help prevent or treat bleeding, transfuse as needed to maintain target platelet count.

Response:

Measure platelet count from 10 minutes to 3 hours after transfusion. Generally, expect an adult platelet count increment of approximately 7-10,000/ mm^3 for each RDP given, or 30-60,000/ mm^3 for each SDP given. In neonates and infants, a dose of 5-10 mL/kg of platelets (RDP or SDP) should result in a 50-100,000/mm^3 increment.

At least 7.1 x 10^9 platelets/L are consumed daily in endothelial support functions, the equivalent of approximately one RDP daily for a 70 kg adult with marrow failure.

Response to platelet transfusion is adversely affected by the presence of fever, sepsis, splenomegaly, severe bleeding, consumptive coagulopathy, HLA alloimmunization and treatment with certain drugs (e.g., amphotericin B).

Ref. 9, 41, 50, 51

Indications and Contra-indications:

Use to treat bleeding due to critically decreased circulating platelet counts or functionally abnormal platelets.

Use prophylactically to prevent bleeding at pre-specified low platelet counts. In general, maintain platelet count >10,000/mm^3 in stable, non-bleeding patients, >20,000/mm^3 in unstable non-bleeding patients and >50,000/mm^3 in patients undergoing invasive procedures or actively bleeding.

Do not use in patients with autoimmune thrombocytopenia or thrombotic thrombocytopenic purpura except for life-threatening hemorrhage.

For complete Side Effects and Hazards see appendix.

Ref. 19

PLATELETS | UTILIZATION GUIDELINES

Perioperative/Periprocedural

Cardiothoracic Surgery:

a) Routine prophylactic transfusions are not required in the absence of bleeding.
b) When coagulation parameters are not significantly abnormal, counts <100,000/mm^3 accompanied by major unexpected microvascular bleeding are appropriately treated with platelet transfusion.

Other Surgical Procedures:

a) Intraoperative platelet counts should be obtained to guide transfusion. Microvascular bleeding in the setting of potential dilutional thrombocytopenia may require empiric transfusion before counts are available.
b) Prophylactic preoperative transfusion is rarely required for counts >100,000/mm^3, is usually required for counts <50,000/mm^3 and is guided by risk factors for intermediate counts.
c) Procedures with insignificant blood loss or vaginal deliveries can be performed at counts <50,000/mm^3 without prophylactic transfusion.
d) Neurologic or ophthalmologic procedures require a platelet count near 100,000/mm^3.
e) Transfusion may be required with apparently adequate counts when known or suspected platelet dysfunction results in microvascular bleeding.

Specific Procedures:

a) When prophylactic transfusion is deemed necessary, a post-transfusion count should be obtained to assure an appropriate increment before performance of the procedure.
b) In the absence of other coagulopathy, major invasive procedures require platelet counts of at least 40,000 to 50,000/mm^3 (including CVP placement, paracentesis / thoracentesis, respiratory tract / GI biopsies, closed liver biopsy, lumbar puncture, sinus aspiration & dental

extraction).
c) A threshold of 80,000/mm^3 has been proposed for spinal epidural anesthesia.
d) Fiberoptic bronchoscopy without biopsy by an experienced operator may be safely performed in the presence of a platelet count <20,000/mm^3.
e) GI endoscopy without biopsy may be safely performed at platelet counts <20,000/mm^3.

Platelet Function Defects:

Patients with congenital or acquired defects in platelet function may be transfused for critical bleeding or before major surgery regardless of the platelet count. Transfusion is generally not indicated when platelet dysfunction is extrinsic to the platelet (e.g., uremia, certain types of von Willebrand Disease, hyperglobulinemia) since transfused platelets function no better than the patient's own platelets. When platelet surface glycoproteins are missing (e.g., Glanzmann Thrombasthenia, Bernard-Soulier Syndrome), transfusion should be undertaken only when more conservative efforts to manage bleeding fail since alloimmunization may cause future life-threatening refractoriness.

Antiplatelet Agents:

Thienopyridine platelet ADP receptor inhibitors and direct glycoprotein IIb/IIIa inhibitors impair platelet function. Platelets should not be transfused prophylactically without thrombocytopenia, but high dose therapeutic transfusion may be required for life-threatening hemorrhage in patients on these drugs.

Neonates:

Neonates undergoing invasive procedures / minor surgery or experiencing clinically significant bleeding may be transfused at <50,000/mm^3. For major surgery or bleeding in the face of additional hemostatic stressors (e.g., disseminated intravascular coagulation, necrotizing

enterocolitis) transfusion is appropriate at counts <100,000/mm^3.

Ref. 4, 5, 7, 9, 20, 29, 42

Critical Care:

Massive Transfusion:
A transfusion target of >50,000/mm^3 is recommended for acutely bleeding patients and >100,000/mm^3 for those with multiple trauma or CNS injury. The platelet count may fall below 50,000/mm^3 when >1.5–2 blood volumes have been replaced with red cells. In the presence of microvascular bleeding, transfusion may be appropriate when counts are known or suspected to be <100,000/mm^3.

Disseminated/Local Intravascular Coagulation (DIC/LIC) and/or Sepsis:
Microvascular bleeding is treated in children and adults with platelet counts <50,000/mm^3 or neonates <100,000/mm^3.

Neonates:
A prophylactic transfusion trigger of <20,000/mm^3 for stable neonates at term, or <30,000/mm^3 for stable premature neonates, is justified. High-risk neonates (those with extremely low birthweight, perinatal asphyxia, sepsis, ventilatory assistance with an FIO_2>40% or clinical instability) may be transfused at <30,000/mm^3 at term or <50,000/mm^3 if premature.

Infants on extracorporeal membrane oxygenators (ECMO) are usually transfused to maintain a platelet count >100,000/mm^3.

Ref. 7, 8, 14, 29, 40, 43, 46, 55

Hematology/Oncology:

Acute Leukemia and Following High Dose Chemotherapy:

A prophylactic transfusion trigger of ≤10,000/mm^3 may be used for stable patients, except as noted below. Patient-specific clinical data may increase the threshold at which prophylactic transfusion is desirable (e.g., major/minor bleeding, coagulopathy, drug-induced platelet dysfunction, fever/sepsis, hyperleukocytosis, planned procedures, use of antithymocyte globulin, serious mucositis or cystitis, acute graft-versus-host disease, liver dysfunction/veno-occlusive disease or rapid decline in counts). Prophylactic platelets may also be given at higher counts when availability of compatible platelet products is reduced (e.g., short-dated matched units).

Higher-than-usual doses of platelets result in longer intervals between transfusions which may be of value in the outpatient setting.

Therapeutic transfusion for major bleeding should maintain counts ≥50,000/mm^3.

Chemotherapy for Solid Tumors:

The usual prophylactic transfusion trigger is ≤10,000/mm^3. The greater risk of bleeding from bladder neoplasms / necrotic tumors and the serious impact of even minor bleeding in patients with limited physiologic reserve may warrant a transfusion trigger of ≤20,000/mm^3.

Transfusion Refractoriness:

a) Post-transfusion platelet counts obtained 10-60 minutes after infusion should be obtained whenever possible. The 10-60 minute post infusion count measures transfusion recovery which is most sensitive to immune platelet destruction. Post-infusion counts at 24 hours assess platelet survival, which is more sensitive to non-immune factors such

as sepsis, splenomegaly, DIC, etc. The American Society of Clinical Oncology recommends that additional products be given if post transfusion counts are unacceptable.

b) Alloimmune refractoriness is more likely in the setting of at least two consecutive poor platelet increments at 10-60 minutes after transfusion. Alloimmunization should be confirmed by demonstration of antibodies to platelets (e.g., to human leukocyte antigens [HLA] or human platelet antigens [HPA]). Single donor products identified by HLA/HPA matching and/or crossmatching should be transfused. In the absence of HLA/HPA-compatible products, fresh ABO-compatible units are preferred.

c) The incidence of HLA alloimmunization has been shown to be reduced by the use of leukoreduced blood products (platelets and RBCs) in any patient expected to receive multiple platelet transfusions during the course of therapy.

d) Severely alloimmunized patients who do not respond to available matched products do not benefit from unmatched prophylactic platelet transfusions and should only be transfused for active bleeding.

Idiopathic Thrombocytopenic Purpura (ITP):

a) Patients who experience major, life-threatening bleeding or intraoperative hemorrhage should receive high-dose platelet transfusions.

b) Prophylactic transfusions are usually inappropriate since transfused platelets do not survive any longer than patients' native platelets. Transfusion may be considered before elective splenectomy with platelet counts $\leq 10{,}000/mm^3$.

Thrombotic Thrombocytopenic Purpura (TTP) and Heparin-Induced Thrombocytopenia with Thrombosis (HITT):

Due to the significant risk of fatal thrombosis, platelets

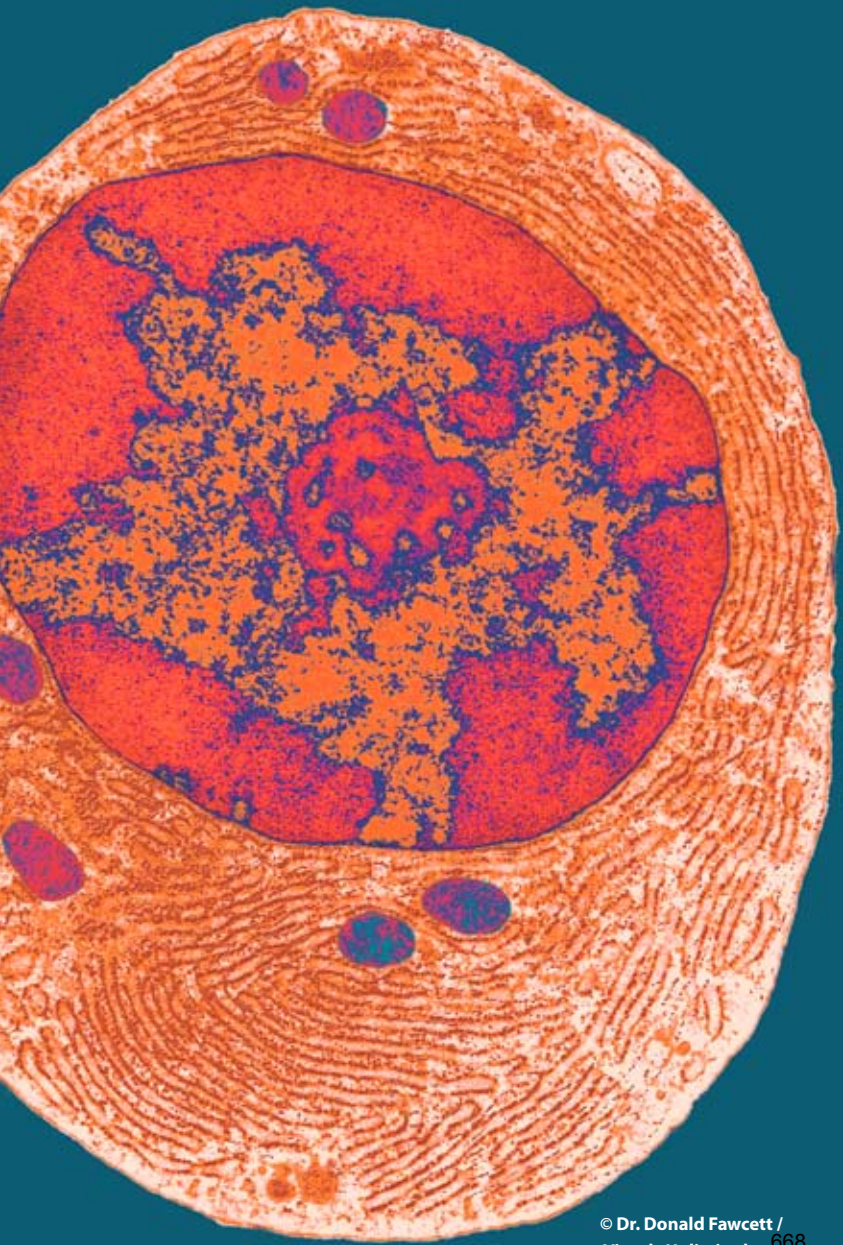
should only be transfused in the setting of life-threatening hemorrhage.

Post-Transfusion Purpura (PTP):
Platelets may be used therapeutically for severe bleeding. Transfusion of randomly selected platelets is usually ineffective. Though efficacy is not well documented, human platelet antigen (HPA)-1a (PI^{A1})-negative platelets are frequently given empirically while specific alloantibody testing is in progress. High-dose intravenous immunoglobulin is the treatment of choice for PTP.

Neonatal Alloimmune Thrombocytopenia (NAIT):
Platelets should lack the HPA recognized by circulating maternal antibodies, although concentrates from random donors may be effective when matched platelets are unavailable. If maternal platelets are used, they should be washed or volume-reduced and irradiated.

Aplastic Anemia:
Transfuse stable patients prophylactically at counts ≤5,000/mm^3 and patients with fever or minor hemorrhage at counts 6,000-10,000/mm^3.

Ref. 7, 9, 13, 14, 15, 20, 21, 41, 42, 43, 50



FROZEN PLASMA | GENERAL INFORMATION

Components:

Approved name: Fresh frozen plasma, Fresh frozen plasma donor retested, Plasma frozen within 24 hours after phlebotomy, Plasma cryoprecipitate reduced.

Also referred to as FFP, FP24, plasma or cryo poor plasma.

Preparation variations include:
Thawed Plasma, Liquid Plasma.

Description of Components:

Plasma consists of the noncellular portion of blood that is separated and frozen after donation. It may be prepared from whole blood or collected by apheresis. The anticoagulant solution used and the volume are indicated on the label. The volume of the unit is approximately 250 mL but variation may be expected. FFP is frozen at -18C or colder within 6-8 h of collection (depending upon the anticoagulant) and contains functional quantities of all coagulation factors. Plasma frozen within 24 hours (FP24) and thawed plasma may contain variably reduced levels of Factor V and Factor VIII, Despite these differences, FP24, thawed plasma and FFP are generally used for the same indications.

Plasma, cryoprecipitate reduced contains 20-30% reduced levels of Factor VIII, von Willebrands' factor, fibrinogen, fibronectin and Factor XIII.

By convention, 1 U of a coagulation factor is defined as that activity present in each milliliter of a standard pool of plasma units.

Ref. 15, 35, 37

Selection and Preparation:

Plasma for transfusion must be ABO-compatible with the recipient's red cells, for example, group A Plasma is suitable for group A and group O patients. Group AB Plasma is suitable for all blood types. Frozen Plasma must be thawed, usually in a water bath, and infused immediately or stored at 1-6°C for up to 24 hours. FFP and FP24 may be relabeled as Thawed Plasma and used as a source of stable coagulation factors for up to 5 days, unless it was collected by apheresis in an open collection system. Plasma, cryoprecipitate reduced is indicated in the treatment of Thrombotic Thrombocytopenic Purpura (TTP).

Ref. 19, 35, 37

Dosing:

The dose of plasma is determined by the patient size and clinical condition. When used to correct multiple coagulation factor deficiencies, plasma transfusion should be guided by coagulation testing. A prothrombin time (PT) greater than 1.5 times the mid-range of normal, an activated partial thromboplastin time (APTT) greater than 1.5 times the top of the normal range, or factor assay less than 25%, can be used as thresholds at which therapeutic or prophylactic replacement may be indicated in an appropriate clinical setting. When such testing is not readily available, clinical evidence of bleeding may be used to direct transfusion decisions. Plasma should be administered in doses calculated to achieve a minimum of 30% of plasma factor concentration. This is usually achieved with the administration of 10-20 mL/kg, though more may be required depending upon the clinical situation.

When used to correct isolated coagulation factor deficiencies for which no concentrated preparation is available (e.g., factor V, or XI), dosing will depend on the half-life of the specific factor, the pretransfusion

level of the factor, the desired post transfusion level and the duration of raised levels required.

Ref. 7, 18, 38

TTP initially requires exchange of 1 – 1.5 plasma volume daily and may need to be increased to twice-daily single plasma volume exchanges in refractory patients. The volume and/or frequency of exchange may be tapered as disease activity declines.

Response:

Frozen Plasma used to correct coagulation abnormalities should stop bleeding and bring the APTT and PT within the hemostatic range, but transfusion will not always correct these values, or the correction may be transient.

Frozen Plasma used to treat TTP should result in an increasing platelet count associated with a decrease in serum lactate dehydrogenase.

Indications and Contra-indications:

Frozen Plasma is indicated for use in patients with the following conditions:

1. Active bleeding due to deficiency of multiple coagulation factors, or risk of bleeding due to deficiency of multiple coagulation factors.
2. Severe bleeding due to warfarin therapy, or urgent reversal of warfarin effect
3. Massive transfusion with coagulopathic bleeding.
4. Bleeding or prophylaxis of bleeding for a known single coagulation factor deficiency for which no concentrate is available.
5. Thrombotic thrombocytopenic purpura.
6. Rare specific plasma protein deficiencies, such as C1-inhibitor.

Frozen Plasma should not be used for

1. Increasing blood volume or albumin concentration
2. Coagulopathy that can be corrected with administration of Vitamin K.
3. Normalizing abnormal coagulation screen results, in the absence of bleeding.

For complete Side Effects and Hazards see appendix.

Ref. 1, 7, 15

FROZEN PLASMA | UTILIZATION GUIDELINES

Perioperative:

Warfarin and Liver Disease:
Frozen Plasma may be used to treat multiple coagulation factors (e.g., liver disease) prior to an invasive procedure that would create a risk of bleeding. However, the response may be unpredictable and complete normalization of the hemostatic defect does not occur. Patients with liver disease or those taking warfarin may safely undergo operative or invasive procedures when the PT is ≤1.5 times mid-range normal.

Frozen Plasma is indicated for patients on warfarin only if there is serious bleeding or urgent reversal of warfarin effect is necessary. Other patients can be treated simply with withdrawal of warfarin and administration of vitamin K.

Factor Deficiency:
Prophylactic correction of a known factor deficiency for which specific concentrates are unavailable is guided by recommended perioperative hemostatic levels for each type of procedure.

Massive Transfusion and Cardiopulmonary Bypass:
Frozen Plasma may be used to treat excessive microvascular bleeding, as determined on visual assessment of the operative field jointly by the anesthesiologist and surgeon when the coagulation screening test results are abnormal or not available in a timely fashion. However, microvascular bleeding may be a result of hypofibrinogenemia or residual heparin effect.

Ref. 7, 18, 38, 47

Oncology: See Critical Care

Critical Care:

Warfarin:

Patients on warfarin who experience serious bleeding are treated with Vitamin K (at a dose determined by the INR) and Frozen Plasma or prothrombin complex concentrates as clinically warranted.

Acute Disseminated Intravascular Coagulation:

Addressing the underlying cause is the foundation of treatment, and the patient is supported with transfusion of Frozen Plasma in combination with Platelets and Cryoprecipitate. If there is no bleeding, blood products are not indicated prophylactically, regardless of the results of laboratory tests.

Thrombotic Thrombocytopenic Purpura:

If plasma exchange is not immediately available, simple transfusion of plasma can be a useful alternative until exchange can be started.

Ref. 7, 18, 38

Hematology:

Specific Plasma Protein Deficiencies:
Deficiencies of other isolated plasma proteins and factors in a setting where concentrates are not readily available are also treated with Frozen Plasma:

a) Treatment or prophylaxis of thromboembolism in antithrombin, protein C and protein S deficiencies.
b) Heparin resistance (antithrombin III deficiency) in a patient requiring heparin
c) Therapy of acute angioedema or preoperative prophylaxis in hereditary C1-inhibitor deficiency.

Ref. 7, 18, 38

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OGEN

Components:

Approved names: Cryoprecipitated Antihemophilic Factor (AHF); Cryoprecipitated AHF, Pooled.

Also referred to as cryoprecipitate, cryoprecipitate pool, cryo, pooled cryo.

Description of Components:

A cryoprecipitate unit is prepared by thawing one unit of FFP between 1-6°C and recovering the cold insoluble precipitate. The cryoprecipitate is refrozen within 1 hour.

If the label indicates "Cryoprecipitated AHF, Pooled," several units of cryoprecipitate have been pooled into one bag, and the volume of the pool is indicated on the label.

Cryoprecipitate contains concentrated levels of fibrinogen, Factor VIII:C, Factor VIII:vWF (von Willebrand factor), Factor XIII, and fibronectin.

Each unit of cryoprecipitate should contain at least 80 IU Factor VIII:C and 150 mg of fibrinogen in 5-20mL of plasma.

Selection and Preparation:

Cryoprecipitate is considered to be an acellular blood component. Compatibility testing is unnecessary. Rh type need not be considered. It is preferable to use cryoprecipitate that is ABO-compatible with the recipient's red cells.

CMV testing and leukoreduction are not required. Frozen cryoprecipitate is thawed in a protective plastic overwrap in a waterbath at 30-37°C up to 15 minutes. Thawed cryoprecipitate should be kept at room temperature and transfused as soon as possible after thawing or within 6 hours if it is a closed single unit or has been pooled prior to freezing. It should be transfused within 4 hours if it is

an open system or units have been pooled after thawing.

For pooling, the precipitate in each unit should be mixed well with 10 –15 mL of diluent (0.9% Sodium Choride, Injection USP) to ensure complete removal of all material from the container. Cryoprecipitate pooled prior to freezing requires no extra diluent.

Dosing:

The number of cryoprecipitate units can be estimated by using the following calculation

- Weight (Kg) x 70mL/Kg = blood volume (mL)
- Blood volume (mL) x (1.0-hematocrit) = plasma volume(mL)
- fibrinogen required (mg) = (desired fibrinogen level (mg/dL) - initial fibrinogen level (mg/dL)) multiplied by (plasma volume (mL) divided by 100).
- Bags of cryo required = mg fibrinogen required divided by 250 mg fibrinogen per bag of cryo.

The frequency of dosing depends on the half-life and recovery of the coagulation factor that is being replaced (check factor levels).

A typical dose for the treatment of hypofibrinogenemia is one cryoprecipitate unit per 7 - 10 kg of body weight.

Ref. 15

Response:

Pretransfusion and posttransfusion coagulation factor levels should be determined to assess the adequacy of the cryoprecipitate dose.

One unit of cryoprecipitate per 10 kg of body weight raises plasma fibrinogen concentration by ~ 50 mg/dL in the absence of continued consumption or massive bleeding (assuming minimum fibrinogen content per bag of cryo).

Indications and Contra-indications

Cryoprecipitate is indicated for bleeding associated with fibrinogen deficiencies and Factor XIII deficiency.

Patients with hemophilia A or von Willebrand's disease (vWD) should only be treated with cryoprecipitate when appropriate Factor VIII concentrates or Factor VIII concentrates containing FVIII: vWF are not available.

Do not transfuse cryoprecipitate unless laboratory studies confirm deficiency of a specific clotting protein for which this component is indicated (e.g. fibrinogen).

For complete Side Effects and Hazards see appendix.

Ref. 15

Perioperative:

Fibrin Sealant:
Both autologous and allogeneic cryoprecipitate units have been used in the preparation of fibrin sealant for topical use, but commercially produced, viral inactivated fibrin sealant is preferable with respect to safety and efficacy.

Ref. 58

Oncology:

Hypofibrinogenemia / dysfibrinogenemia:
Transfuse for bleeding associated with fibrinogen levels <100 to 120 mg/dL or reduced functional levels of fibrinogen.

Ref. 22

Critical Care

Cryoprecipitate is especially useful when it is not possible to give enough FFP to provide adequate levels of fibrinogen without volume overloading the patient.

Cryoprecipitate has been used for uremic bleeding, but efficacy has not been clearly demonstrated, and 1-deamino-8-D-arginine vasopressin (DDAVP) and other modalities are preferred.

Cryoprecipitate should not be used in the critical care setting as a source of fibronectin to improve reticuloendothelial system function.

Massive Transfusion:
Transfuse for bleeding in massively transfused patients when the fibrinogen level is documented to be <100 mg/dL. This not likely to occur until after ~1 1/2 blood volumes are replaced.

Hypofibrinogenemia / dysfibrinogenemia:
Transfuse for bleeding. Most cases of hypofibrinogenemia/ dysfibrinogenemia in critical care

are associated with DIC or hepatic insufficiency.

Ref. 31

Hematology

Congenital fibrinogen deficiencies are uncommon, and are variably associated with bleeding. The treatment of patients with an isolated fibrinogen deficiency should be reserved for episodes of clinical bleeding, or when there is a significant risk of bleeding complications due to an invasive procedure or pregnancy.

For hemophilia A or vWD, cryoprecipitate should only be used if appropriate recombinant or virus- inactivated Factor VIII or Factor VIII:vWF concentrates are not available. DDAVP is the treatment of choice for type 1 vWD.

Congenital afibrinogenemia / Congenital and acquired dysfibrinogenemia:
Transfuse for bleeding or risk of bleeding associated with a fibrinogen level <100 mg/dL by a quantitative or functional assay.

Factor XIII deficiency (Rare):

a) Transfuse for bleeding and prophylaxis.
b) Factor XIII deficiency is rare, and characterized by bleeding and poor wound healing.
c) Factor XIII has a half-life of 4 to 14 days, and only ~ 1-5% activity levels are needed to control bleeding. Newborns with Factor XIII deficiency should be placed on a prophylactic regimen of replacement therapy because of the high incidence of intracranial hemorrhage.
d) Virus inactivated Factor XIII concentrates are preferred for the treatment of Factor XIII deficient patients, but are not readily available. Cryoprecipitate can be given in doses of one bag per 10-20 kg of body weight every 3 to 4 weeks. FFP can also be used.

Ref. 4, 8, 15, 31

ROLE OF THE HOSPITAL TRANSFUSION COMMITTEE

Description:

Hospitals are required by accrediting and regulatory agencies (e.g., Joint Commission, AABB and College of American Pathologists) to ensure appropriate use of blood products. The Code of Federal Regulations (CFR) requires a hospital to develop, implement, and maintain an effective, ongoing, hospital-wide, data-driven quality assessment and performance improvement program. A hospital's transfusion practices should fall under such a program. How this is accomplished may vary from hospital to hospital. Some maintain a Transfusion Committee dedicated solely to this function. Others may charge a Quality Assurance Committee or a Blood and Tissue Committee with this task. For the most part, the accrediting and regulatory agencies do not specify how this peer review function is accomplished, as long as it is being performed.

The responsible committee should address through review or audit the following aspects of blood utilization (list may not be all inclusive):

01. Blood ordering practices
02. Blood refusal practices
03. Patient identification
04. Sample collection and labeling
05. Pretransfusion testing orders
06. Distribution, handling and dispensing
07. Blood administration policies
08. Infectious and non-infectious adverse events
09. Monitoring of patients for appropriate responses
10. Medical errors, near misses and sentinel events
11. Appropriate utilization
12. Wastage and discard rates
13. Ability of transfusion services to meet patient needs
14. Clinical alternatives to blood transfusion (perioperative salvage)

Membership and Structure:

This multidisciplinary committee should include representatives from the Medical Staff (surgery, anesthesia, medicine, hematology, pediatrics), Nursing, Hospital Administration, the Transfusion Service and other interested parties as applicable. Confidentiality rules apply. If guests are invited, they may be excused during discussions with potential liability issues. The Medical Director of the Transfusion Service is a vital member of the committee who may or may not serve as chairperson. The chairperson should, however, be a physician knowledgeable in transfusion medicine.

The committee should establish guidelines for administration of each of the blood components transfused in the institution, using current medical literature as a resource.

The transfusion guidelines should be approved by the Medical Staff prior to implementation. Transfusion guidelines are intended to remind ordering physicians of the transfusion practices for which there is general support and clinical trial evidence. Guidelines cannot be expected to cover every instance in which a transfusion is indicated. In every case, however, the rationale for transfusion should be clearly documented in the medical record.

Process:

The review of transfusions can be done prospectively by transfusion service personnel (before blood is issued) or retrospectively by the Transfusion Committee (after blood is issued) for certain high cost blood products, prospective review may be appropriate to prevent unnecessary transfusions. Similarly, prospective review of potentially inappropriate orders, for example, an order for platelet transfusion to a patient with thrombotic thrombocytopenic purpura or an order for four units of red blood cells for a child, may also require review prior to blood issue. For most transfusions and blood products,

however, involving large numbers of transfusions and patients, retrospective reviews are adequate and most commonly used.

For each transfusion, the following information should be documented:
1. Physician order
2. Indication for transfusion
3. Informed patient consent
4. Patient identification checks
5. Blood component issuance documentation
6. Patient monitoring during transfusion
7. Assessment of patient outcome
8. Applicable lab or clinical results before and after transfusion

Trained hospital quality assurance or compliance staff can do chart or electronic record reviews, using the approved transfusion guidelines developed by the committee. When there are questions about the indications and results of a transfusion, the clinical records should be peer reviewed or reviewed at the transfusion committee meeting.

If the transfusion committee is unable to determine a justification for the transfusion, the patient's physician should be contacted for additional information. If the additional information does not justify the transfusion; there is an opportunity to educate the patient's physician. If the letter is ignored or if repeated unjustified transfusion practices are noted, a department chair or credentialing committee may need to be involved in the review process.

Monitors:

Blood usage should be monitored by whichever parameters are most useful for the institution: by physician, by clinical department, by diagnosis (Diagnosis-Related Groups), or by surgical procedures In addition, the Transfusion Committee must ensure that blood is administered correctly. Before a transfusion

is given there must be informed consent according to the institutional procedures, confirmation that the component is intended for the patient and is not expired, and verification of the patient's identity.

The wastage of all blood components, both allogeneic and autologous, should be monitored. The committee should review adverse reactions to blood products. The committee must also ensure that a mechanism exists for reporting and evaluation of suspected transfusion-transmitted diseases.

Reports:

The Transfusion Committee or its equivalent, should document activities by minutes and generate reports of its work for submission to other entities of the hospital (e.g., clinical departments of the Medical Staff, the Medical Staff Executive Committee, the Clinical Practices Committee, the Credentials Committee). The intent of this reporting is to provide other peer review committees with the results of reviews of transfusion related patient care. These minutes can be protected from inappropriate legal discovery as a critical component of an institutions quality monitoring program.

Summary:

Hospitals are required to review blood transfusion practices and adverse outcomes. Accrediting and regulatory agencies do not specify how this peer review function is accomplished, as long as it is being performed.

The work of auditing and monitoring blood utilization is not sophisticated. It is simply a matter of having appropriate policies and procedures in place, reviewing and revising them as necessary, and monitoring that they are followed.

Ref. 23, 39, 44, 56

APPENDIX: SIDE EFFECTS AND HAZARDS OF BLOOD TRANSFUSION

The following sections are reproduced from the July 2002 Circular of Information:

A. General

The following side effects and hazards pertain to transfusion of Whole Blood or any component prepared from blood collected from individual donors.

Immunologic Complications, Immediate

1. Hemolytic transfusion reaction, the destruction of transfused red cells, is discussed in detail in the section on red-cell-containing components.

2. *Immune-mediated platelet destruction,* one of the causes of refractoriness to platelet transfusion, is the result of alloantibodies in the recipient to HLA or platelet-specific antigens on transfused platelets. This is described in more detail in the section on Platelets.

3. *Febrile nonhemolytic reaction* is typically manifested by a temperature elevation of ≥ 1 C or 2 F occurring during or shortly after a transfusion and in the absence of any other pyrexic stimulus. This may reflect the action of antibodies against white cells or the action of cytokines, either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may accompany about 1% of transfusions; and they occur more frequently in patients previously alloimmunized by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are due to cytokines in the component, prestorage leukocyte reduction may be beneficial.

4. *Allergic* reactions usually occur as urticaria, but may also include wheezing or angioedematous reactions. No laboratory procedures are available to predict or prevent these reactions, which usually respond to antihistamines or, in severe cases, corticosteroids or epinephrine.

5. *Anaphylactoid reactions,* characterized by autonomic dysregulation, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are a rare but dangerous complication requiring immediate treatment with corticosteroids and epinephrine. The majority of these reactions have been reported in IgA-deficient patients who have IgA antibodies of the IgE class. Such patients may not have been previously transfused and may develop symptoms after infusion of very small amounts of IgA containing plasma, in any blood component.

6. *Transfusion-related acute lung injury (TRALI)* occurs when acutely increased permeability of the pulmonary microcirculation causes massive leakage of fluids and protein into the alveolar spaces and interstitium, usually within 6 hours of transfusion. In many cases, the occurrence of TRALI is associated with the presence of granulocyte antibodies in the donor or recipient. The specific mechanism of action is not clear. Treatment consists of aggressive respiratory support.

Immunologic Complications, Delayed

1. Delayed hemolytic reaction is described in detail in the section on red-cell-containing components.

2. Alloimmunization to antigens of red cells, white cells, platelets, or plasma proteins may occur unpredictably after transfusion. Primary immunization does not become apparent until days or weeks after the immunizing event, and does not usually cause symptoms or physiologic changes. If components that express the relevant antigen are subsequently transfused, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Clinically significant antibodies to red cell antigens will ordinarily be detected by pretransfusion testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can only be detected by specialized testing.

3. Posttransfusion purpura (PTP) is a rare syndrome characterized by the development of dramatic, sudden, and self-limiting thrombocytopenia, typically 7-10 days after a blood transfusion, in a patient with a history of sensitization by either pregnancy or transfusion. While the immune specificity may be to a platelet-specific antigen the patient lacks, autologous and allogeneic platelets are destroyed. In a bleeding patient, high dose Immune Globulin

Intravenous (IGIV) may promptly correct the thrombocytopenia.

4. Graft-vs-host disease (GVHD) is a rare but extremely dangerous condition that occurs when viable T lymphocytes in the transfused component engraft in the recipient and react against tissue antigens in the recipient. GVHD can occur if the host does not recognize as foreign and reject the transfused cells, and can follow transfusion of any component that contains even very small numbers of viable T lymphocytes. Severely immunocompromised recipients are at greatest risk (e.g., fetuses receiving intrauterine transfusions, recipients of transplanted marrow or peripheral blood progenitor cells, and selected patients with severe immunodeficiency conditions), but GVHD has been reported in immunologically normal recipients heterozygous for a tissue antigen haplotype for which the donor is homozygous. This is most likely to occur when the transfused component is from a blood relative or has been selected for HLA compatibility. GVHD remains a risk with leukocyte-reduced components because they contain sufficient residual T lymphocytes. Irradiation of the component renders T lymphocytes incapable of proliferation and is presently the only approved means to prevent GVHD.

Nonimmunologic Complications

1. *Transmission of infectious disease* may occur because this product is made from human blood. This may be due to known or unknown agents, such as viruses. This may occur despite careful selection of donors and testing of blood. Donor selection criteria are designed to screen out potential donors with increased risk of infection with HIV, HTLV, hepatitis, and syphilis, as well as other agents These procedures do not totally eliminate the risk of transmitting these agents. Cytomegalovirus (CMV) may, unpredictably, be present in white-cell-containing components from donors previously infected with this virus, which can persist lifelong despite the presence of serum antibodies. Up to 70% of donors may be anti-CMV positive. Transmission of CMV by transfusion may be of concern in low-birthweight (≤1200 grams) premature infants born to CMV seronegative mothers and in certain other categories of immunocompromised individuals, if they are CMV seronegative. For at-risk recipients, the risk of CMV transmission by cellular components can be reduced by transfusing CMV seronegative or leukocyte-reduced components. For other infectious agents, there are no

routinely available tests to predict or prevent disease transmission. All potential blood donors are subjected to stringent screening procedures intended to reduce to a minimum the risk that they will transmit infectious agents. These organisms include Babesia spp., Bartonella spp., Borrelia spp., Brucella spp., the agent of Colorado tick fever, Leishmania spp., Parvovirus spp., plasmodia, rickettsia, Toxoplasma spp., and certain trypanosomes.

2. *Bacterial contamination* occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever (≥2 C or ≥3.5 F rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction. Platelet components stored at room temperature, previously frozen components thawed by immersion in a waterbath, and red cell components stored for several weeks at 1-6 C have been implicated. Both gram-positive and gram-negative organisms have been identified as causing septic reactions. Organisms capable of multiplying at low temperatures and those using citrate as a nutrient are most often associated with red cell contamination. A variety of pathogens, as well as skin contaminants, have been found in platelet concentrates. Endotoxemia in recipients has resulted from multiplication of Yersinia enterocolitica in stored red-cell-containing components. Prompt recognition of a possible septic reaction is essential, with immediate discontinuation of the transfusion and aggressive therapy with broad-spectrum antimicrobials and vasopressor agents, if necessary. In addition to prompt sampling of the patient's blood for cultures at several different temperatures, investigation should include examination of material from the blood container by Gram's stain, and cultures of specimens from the container and the administration set.

3. *Circulatory overload,* leading to pulmonary edema, can occur after transfusion of excessive volumes or at excessively rapid rates. This is a particular risk in the elderly and in patients with chronic severe anemia in whom low red cell mass is associated with high plasma volume. Small transfusion volumes can precipitate symptoms in at-risk patients who already have a positive fluid balance. Pulmonary edema should be promptly and aggressively treated, and infusion of colloid preparations, including plasma components and the suspending plasma in cellular components, reduced to a minimum.

4. Hypothermia carries a risk of cardiac arrhythmia or cardiac arrest. Rapid infusion of large volumes of cold blood can depress body temperature, and the danger is compounded in patients experiencing shock or surgical or anesthetic manipulations that disrupt temperature regulation. A blood warming device should be considered if rapid infusion of blood is needed. Warming must be accomplished using an FDA-cleared warming device so as not to cause hemolysis.

5. Metabolic complications may accompany large volume transfusions, especially in patients with liver or kidney disease.
   a.) Citrate "toxicity" reflects a depression of ionized calcium due to the presence in the circulation of large quantities of citrate anticoagulant. Because citrate is promptly metabolized by the liver, this complication is rare. Patients with severe liver disease or those with circulatory collapse that prevents adequate hepatic blood flow, may have physiologically significant hypocalcemia after rapid, large-volume transfusion. Citrated blood administered rapidly through central intravenous access may reach the heart so rapidly that ventricular arrhythmias occur. Standard measurement of serum calcium does not distinguish ionized from complexed calcium. Ionized calcium testing or EKG monitoring is more helpful in detecting physiologically significant alteration in calcium levels.
   b.) Other metabolic derangements can accompany rapid or large-volume transfusions, especially in patients with pre-existing circulatory or metabolic problems. These include acidosis or alkalosis (deriving from changing concentrations of citric acid and its subsequent conversion to pyruvate and bicarbonate) and hyper- or hypokalemia.

B. Red Blood Cells

Listed below are hazards specifically to components that contain red cells.

1. *Hemolytic transfusion* reaction is the immunologic destruction of transfused red cells, nearly always due to incompatibility of antigen on the transfused cells with antibody in the recipient's circulation. (See 5 for discussion of nonimmunologic hemolysis.) The most common cause of severe, acute hemolytic reactions is transfusion of ABO-incompatible blood, resulting from identification errors occurring at some point(s) in the transfusion process. Serologic

incompatibility undetected during pretransfusion testing is a much less common cause of acute hemolysis. If a hemolytic reaction is suspected, the transfusion must be stopped and the transfusion service laboratory notified. Information identifying the patient, the transfusion component, and associated forms and labels should be reviewed immediately to detect possible errors. A postreaction blood sample, preferably drawn from a site other than the transfusion access, should be sent to the laboratory along with the implicated unit of blood and administration set. Acute hemolytic reactions characteristically begin with an increase in temperature and pulse rate; symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock. Instability of blood pressure is frequent, the direction and magnitude of change depending upon the phase of the antigen-antibody event and the magnitude of compensatory mechanisms. In anesthetized patients, hypotension and evidence of disseminated intravascular coagulopathy (DIC) may be the first sign of incompatibility. Laboratory findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum bilirubin; in less catastrophic acute hemolytic reactions, a positive direct antiglobulin test (DAT) is commonly found. Treatment includes measures to maintain or correct arterial blood pressure; correct coagulopathy, if present; and promote and maintain urine flow. Rarely, acute hemolytic reactions may not be overtly apparent. Delayed hemolytic reactions occur in previously red-cell-alloimmunized patients in whom antigens on transfused red cells provoke anamnestic production of antibody that reaches a significant circulating level while the transfused cells are still present in the circulation; the usual time frame is 2 to 14 days after transfusion. Signs may include unexplained fever, development of a positive DAT, and unexplained decrease in hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation of lactic dehydrogenase (LDH) or bilirubin may be noted. Most delayed hemolytic reactions have a benign course and require no treatment.

2. Antigens on transfused red cells may cause red cell *alloimmunization* of the recipient, who may experience red cell antibody-mediated reactions to subsequent transfusions. There is no practical way to predict or prevent alloimmunization in any specific transfusion recipient. Clinically significant antibodies to red cell antigens will usually be detected in pretransfusion antibody screening tests.

3. *Circulatory overload,* resulting in pulmonary edema, can accompany transfusion of any component at a rate more rapid than the recipient's cardiac output can accommodate. Whole Blood creates more of a risk than Red Blood Cells because the transfused plasma adds volume without increasing oxygen-carrying capacity. Patients with chronic anemia have increased blood volumes and are at increased risk for circulatory overload.

4. *Iron overload* is a long-term complication of repeated red cell transfusions. Each transfusion contributes approximately 250 mg of iron. Patients requiring multiple transfusions for aplastic anemia, thalassemias, or hemoglobinopathies are at far greater risk than patients transfused for hemorrhagic indications, because blood loss is an effective means of iron excretion. Patients with predictably chronic transfusion requirements should be considered for treatment with iron chelating agents.

5. *Nonimmunologic hemolysis* occurs rarely, but can result from:
   a) introduction of hypotonic fluids into the circulation;
   b) effects of drugs co-administered with transfusion;
   c) effects of bacterial toxins;
   d) thermal injury to transfusion components, by either freezing or overheating;
   e) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies; or
   f) if sufficient physical or osmotic stresses develop, for example, if red blood cells are exposed to excessive heat by non-FDA approved warming methods, mixed with hypotonic solutions or transfused under high pressure through small gauge/defective needles.

C. Platelets

Listed below are hazards that apply specifically to components that contain platelets.

1. *Bacterial Contamination:* Platelet products are the most likely among blood components to be contaminated with bacteria. Gram-positive skin flora are the most commonly recovered bacteria from contaminated platelet units. Symptoms may include high fever (≥2.0 C or ≥3.5 F rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion. Prompt management should include broad-spectrum antibiotic therapy along with cultures of patient sample, suspected

blood component(s), and administration set. Gram's stain of suspected contaminated unit(s) may be helpful.

2. *Platelet Alloimmunization:* Platelets bear a variety of antigens, including HLA and platelet-specific antigens. Patients transfused with platelets often develop HLA antibodies. The patient may become refractory to all but HLA-selected platelets (see "Platelets Pheresis"). When platelets are transfused to a patient with an antibody specific for an expressed antigen, the survival time of the transfused platelets may be markedly shortened. Nonimmune events may also contribute to reduced platelet survival. It is possible to suggest the presence of immune or nonimmune platelet refractoriness by assessing platelet recovery soon after infusion, i.e., 10- to 60-minute postinfusion platelet increment. In immune refractory states secondary to serologic incompatibility, there is poor recovery in the early postinfusion interval. In nonimmune mechanisms (i.e., splenomegaly, sepsis, fever, intravascular devices, and DIC) platelet recovery within 1 hour of infusion may be adequate while longer-term survival (i.e., 24-hour survival) is reduced. Serologic tests can confirm the presence of alloimmunization. Serologic tests may also be helpful in selecting platelets with acceptable survival.

3. *Red Cell Alloimmunization*: Immunization to red cell antigens may occur because of the presence of residual red cells in Platelets. When Platelet units from Rh-positive donors must be given to an Rh-negative female of childbearing potential because of lack of availability of Rh-negative Platelets, prevention of D immunization by use of Rh Immune Globulin should be considered. In some patients, out-of-group Platelets suspended in incompatible plasma that contains anti-A or anti-B may cause a positive DAT and possibly low-grade hemolysis if the recipient's red cells express the corresponding antigen.

D. Fresh Frozen Plasma (FFP)

Antibodies in the plasma may react with the recipient's red cells, causing a positive DAT. In rare instances, TRALI may develop.

E. Cryoprecipitated-AHF

If a large volume of ABO-incompatible cryoprecipitate is used, the recipient may develop a positive DAT and, very rarely, mild hemolysis.

Fatal Transfusion Reactions

When a fatality occurs as a result of a complication of blood or component transfusions, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), should be notified within one FDA business day (telephone: 301-827-6220; e-mail: fatalities2@cber.fda.gov). Within 7 days after the fatality, a written report must be submitted to the Center for Biologics Evaluation and Research (CBER), Director, Office of Compliance and Biologics Quality, ATTN: Fatalities Program Manager (HFM-650), 1401 Rockville Pike, Rockville, MD 20852-1448. A copy of the report should be sent to the collecting facility, if appropriate. Updated information about CBER reporting requirements may be found at: www.fda.gov/cber/transfusion.htm.

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