EE Moore
Denver Health / University of Colorado Denver

Disclosure : Haemonetics, Instrumentation Laboratory, Stago, Prytime & Humacyte
Research Support / Haemonetics Shared IP
Co-founder ThromboTherapeutics Inc
NIH P50 / RM1 / T32 / UMI & DOD Grants

TACTIC

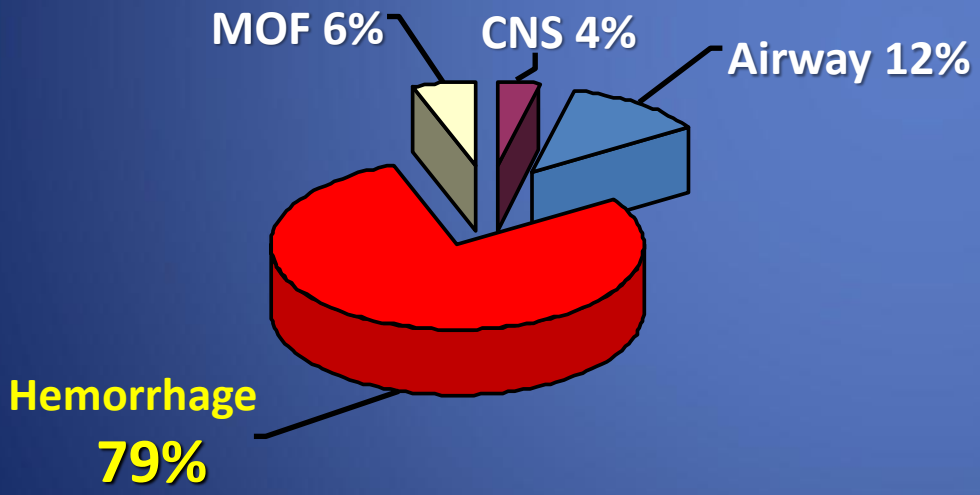
NIH National Heart, Lung, and Blood Institute

DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA

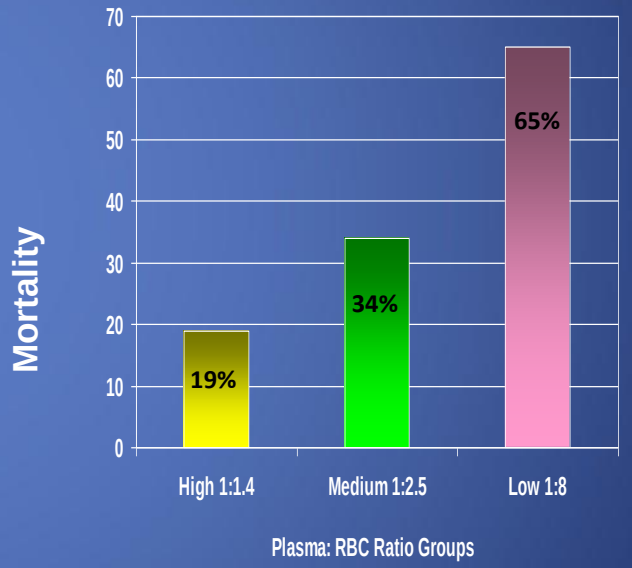
Bleeding is Most Common Preventable Cause of Death: Is Early Plasma the Solution ?

US Military : Potentially Survivable

Iraq Oct 2001 - Nov 2004



FFP : RBC Ratio / 24 Hr – Military Experience



Borgman, Holcomb et al
J Trauma 2007

Plasma is an Effective Multifunctional Colloid

Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock.
Kozar et al. *Anesth Analg* 2011

Restore Endothelial Lining

Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1.
Peng et al. 2013

Reduces Lung Permeability

Plasma is the physiologic buffer of tissue plasminogen activator-mediated fibrinolysis: rationale for plasma-first resuscitation after life-threatening hemorrhage.
Moore et al. JACS 2015

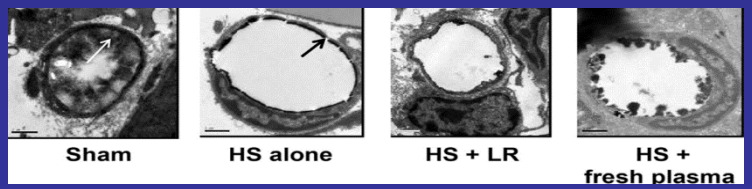
Buffers Fibrinolysis

Plasma-Mediated Gut Protection After Hemorrhagic Shock is Lessened in Syndecan-1-/- MICE.
Ban et al. Shock 2015

Reduces Gut Permeability

Plasma First Resuscitation Reduces Lactate Acidosis, Enhances Redox Homeostasis, Amino Acid and Purine Catabolism in a Rat Model of Profound Hemorrhagic Shock.
D'Alessandro et al. Shock 2016

Enhances Metabolic Recovery



Prehospital Plasma Resuscitation for Hemorrhagic Shock

UNCLASSIFIED

Harmonized Data Collection

»The US DoD and the National Heart Lung and Blood Institute (NHLBI) worked collaboratively on these DoD-funded studies under an interagency strategic plan.

» (Pusateri et al)

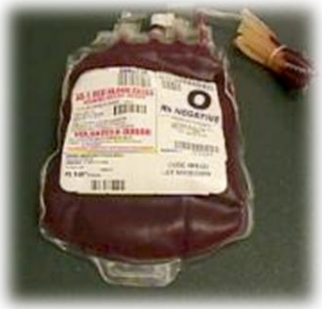
NIH National Heart, Lung, and Blood Institute

»The agreed collaboration included the requirement for the studies to be harmonized in terms of design and data collection, and for samples and data from the studies to be shared

COMBAT Research Study

DENVER HEALTH
Level One Care For ALL

Control Arm	Experimental Arm
1. Normal Saline	1. Plasma Transfusion
2. RBC Transfusion	2. RBC Transfusion
3. Plasma Transfusion	3. Normal Saline



&

Trial Design : Prehospital

Severely injured trauma patients with life-threatening bleeding

SBP < 70 mmHg or SBP < 90 with HR > 108 / min (ROC Study Group)

Estimated 31% mortality in control group

50% Standard Group

50% Experimental Group: Receive Plasma first

Study Objectives

Determine if "plasma first" :

- **Attenuates trauma-induced coagulopathy**
- **Decreases blood product use**
- **Improves metabolic recover**
- **Decreases ARDS, MOF, death**

FDA … 30 day Mortality

PAMPer Trial

P: Prehospital

A: Air

M: Medical

P: Plasma

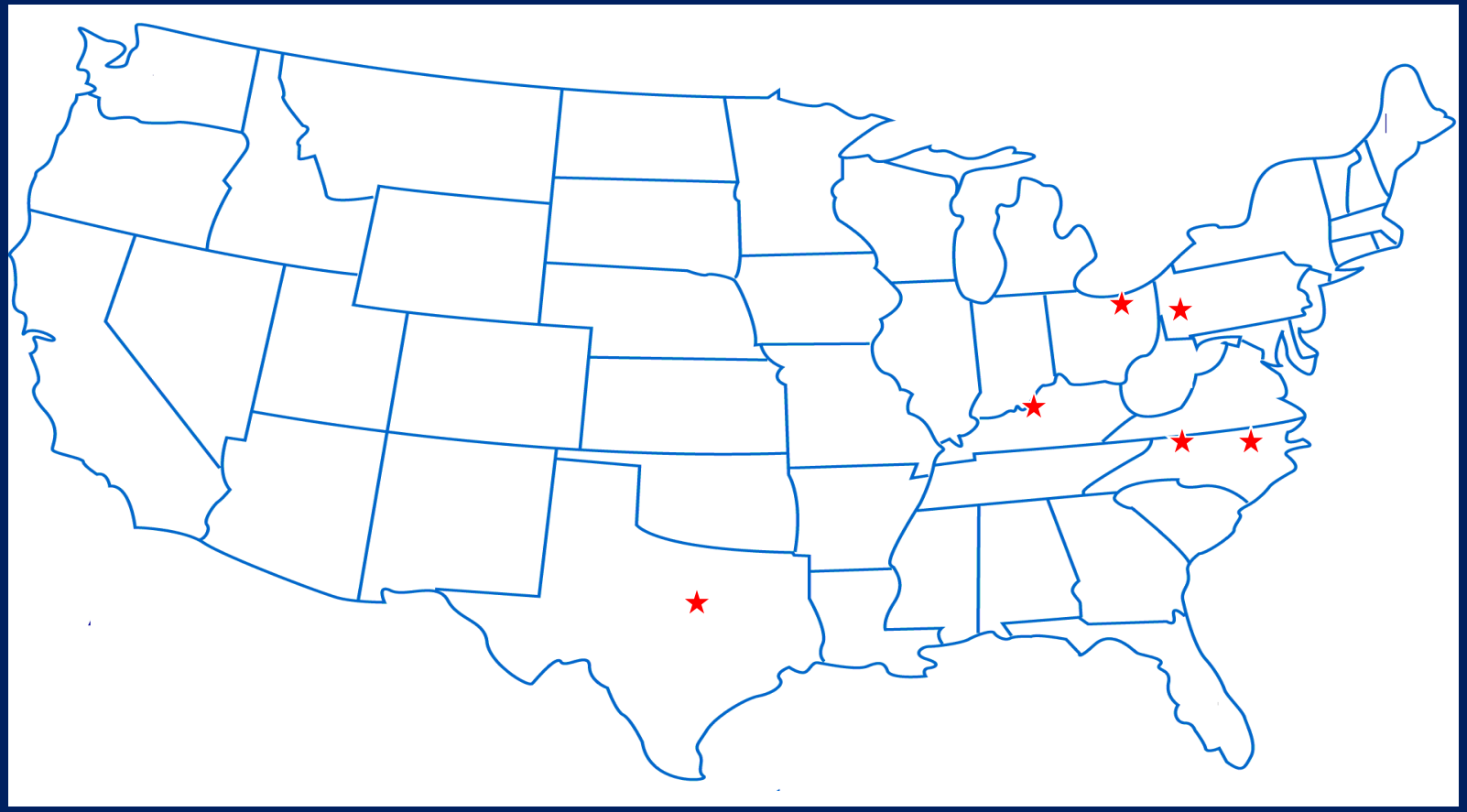
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2018 VOL. 379 NO. 4

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group*

PAMPer Trial



UPMC - Pittsburgh, 2. CWRU MetroHealth - Cleveland, 3. University - Louisville, 4. Vanderbilt Univ - Nashville, 5. UTSW Parkland - Dallas

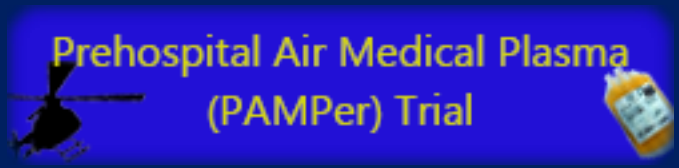
6. Univ Tennessee - Knoxville

Study Population

- **Male** (73%)
- **Blunt** mechanism (82%)
- Median **Injury Severity Score** of 22

- Prehospital **intubation** (51%)
- Prehospital **red blood cell** transfusion (35%)

- Surgeons performed urgent operative **procedures on 58%**



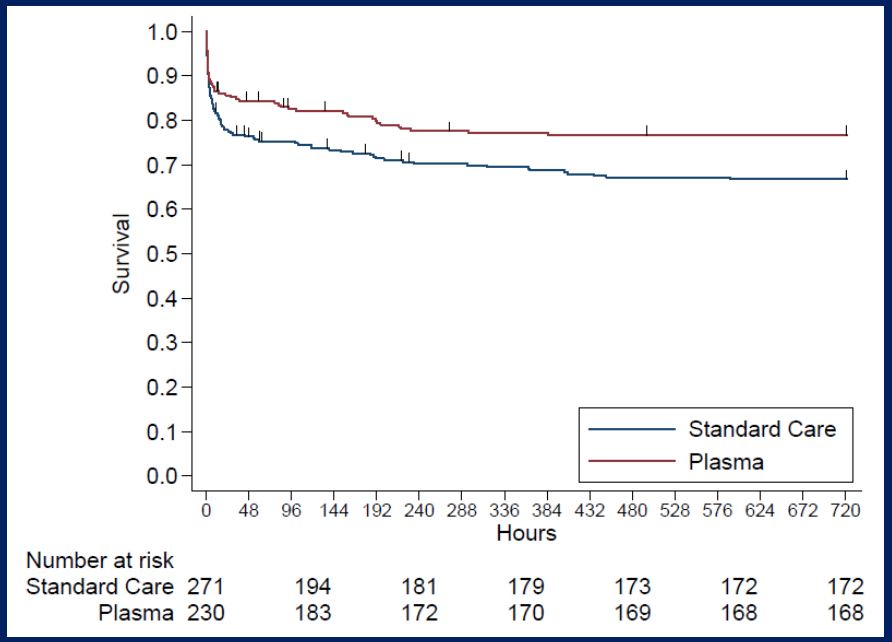
Results

At 30-days … 89 (34.1%) deaths in the standard care group and 53 (24.0%) deaths in the plasma group.

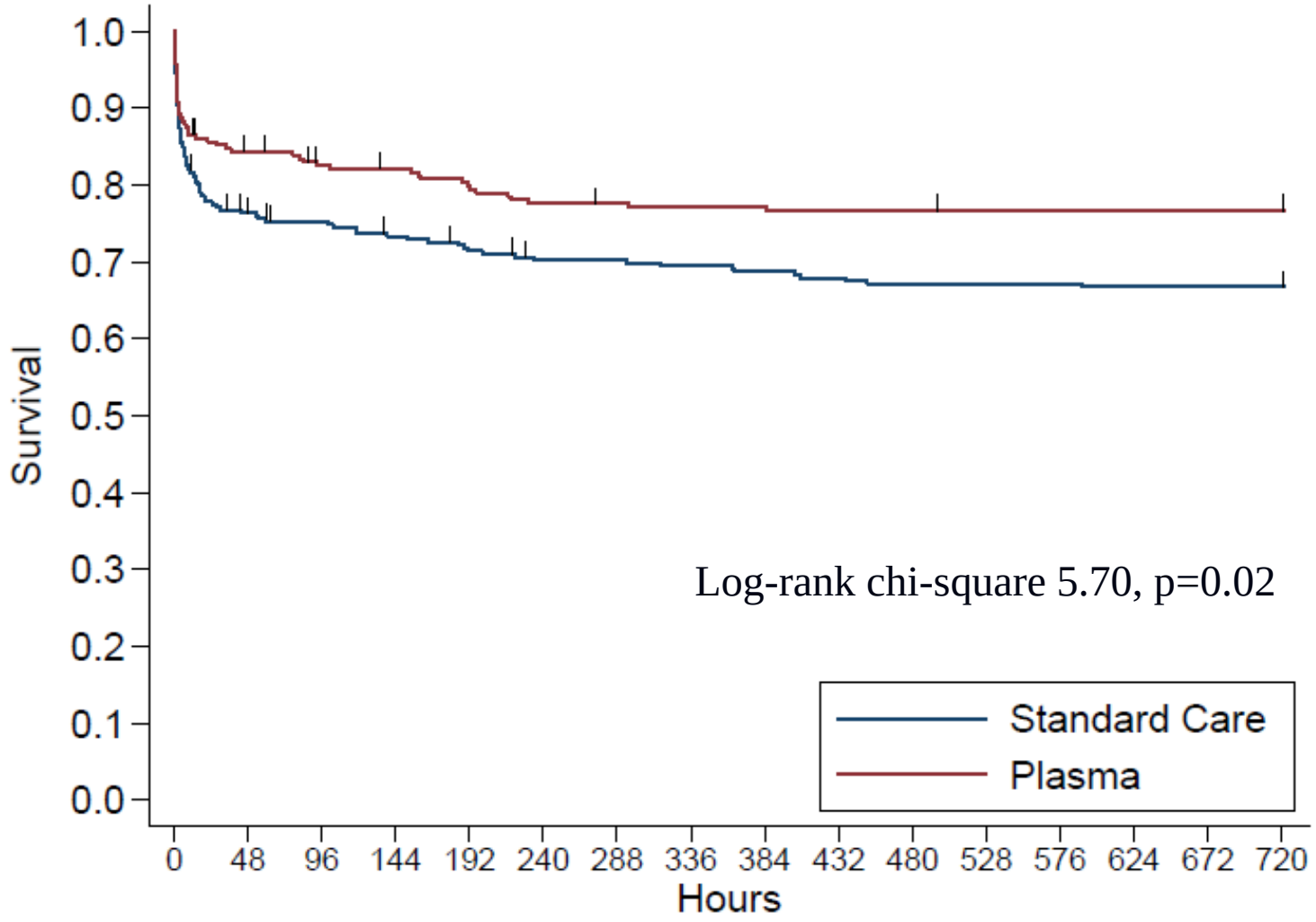
Accounting for intra-cluster variation.

23.2% vs. 33.0%

95%CI -18.6, -1.0; p=0.029



30-Day Mortality



Number at risk							
Standard Care	271	194	181	179	173	172	172
Plasma	230	183	172	170	169	168	168

Control of Major Bleeding after Trauma (COMBAT)

Prospective randomized study of fresh frozen plasma versus crystalloid as initial prehospital fluid resuscitation

Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial

Hunter B Moore MD, Ernest E Moore Prof, Michael P Chapman MD, Kevin McVaney MD, Gary Bryskiewicz, Robert Blechar, Theresa Chin MD, Clay Cothren Burlew MD, Fredric Pieracci MD, F Bernadette West MD, Courtney D Fleming, Arsen Ghasabyan MPH, James Chandler, Christopher C Silliman Prof, Anirban Banerjee Prof and Angela Sauaia Prof

Lancet, The, 2018-07-28, Volume 392, Issue 10144, Pages 283-291, Copyright © 2018 Elsevier Ltd

COMBAT Study Design

Type AB

No Antibodies

(No Pregnancy / Transfusions)

4% ⟶ 1% of Population

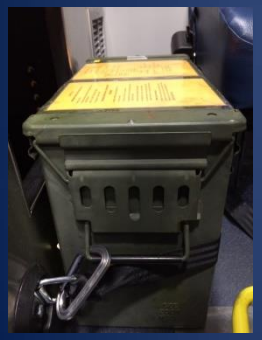
Limited Resource

COMBAT : FP24 Thawing

Plasma Storage

Paramedic Division Freezers - 30° C

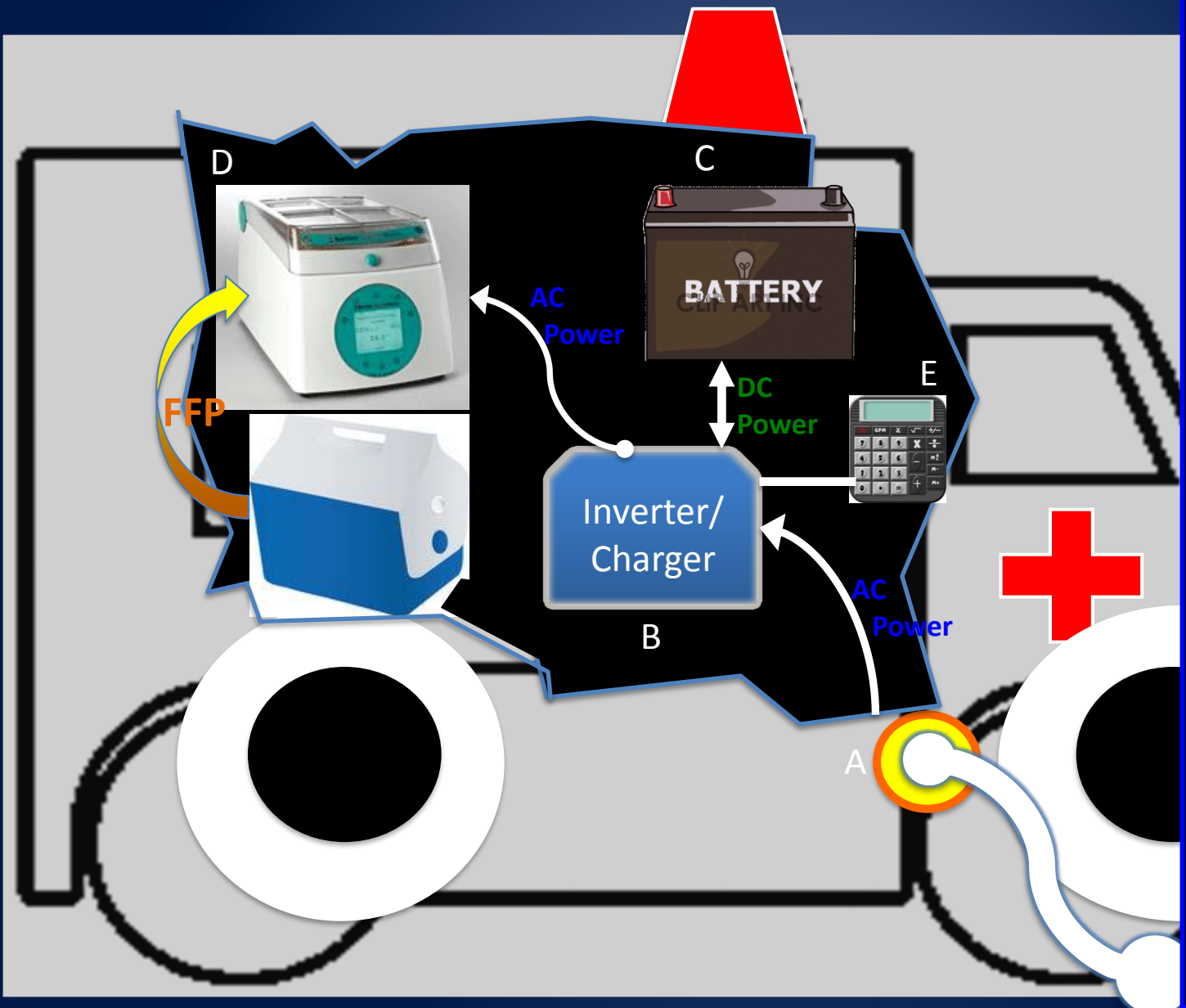
Ambulance Coolers - 18° C



Water Bath (Plasmatherm)

Thaw < 3.5 minutes

Mobile Ambulance Plasma Delivery System



A: Shore power connection, 110 VAC, 20 A, ignition ejector safety and cord reel to GFCI wall receptacle ($1500)

B: Combination 2000 W, 110 VAC power inverter and
100 A, 14.6 VDC battery charger ($1200)

C: 300 Amp-Hour, 12 VDC lithium ion battery with onboard controller ($3000)

D: Plasmatherm Dry Water Bath – can run in continuous modeat 37 °C for 36 hours on battery power ($7000)

E: Charging/power inversion system control panel ($300)

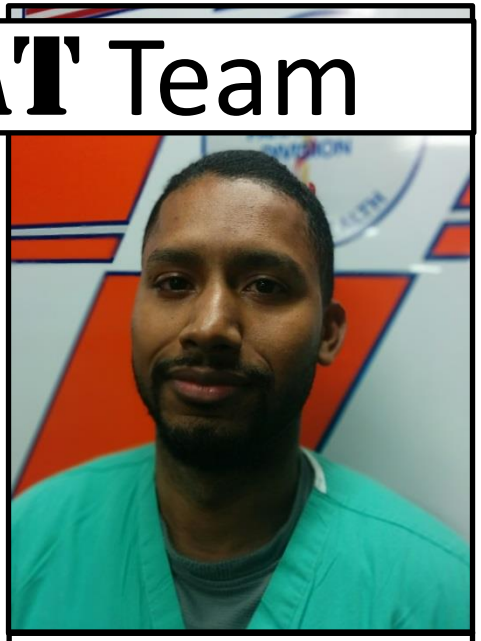
F: FFP storage cooler, vacuum insulated and passively cooled with-23 °C phase change material; rated for ≥72 hours at ≤-18 °C ($600)

Denver EMS Skills / Enthusiasm

COMBAT Team

Arsen Ghasabyan

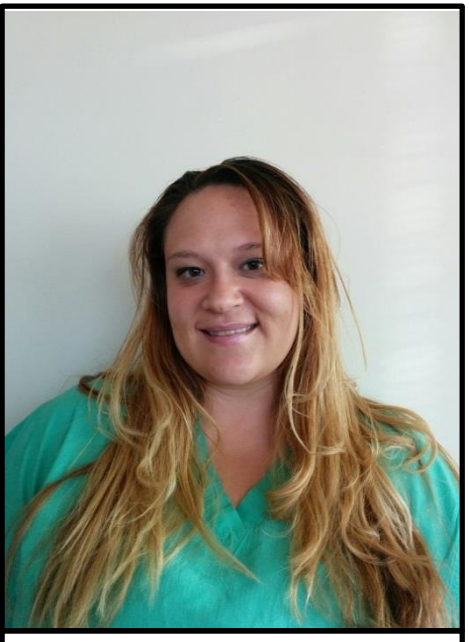
Jim Chandler



Raymond Shepherd-Singh

Courtney Fleming

In hospital 24/7



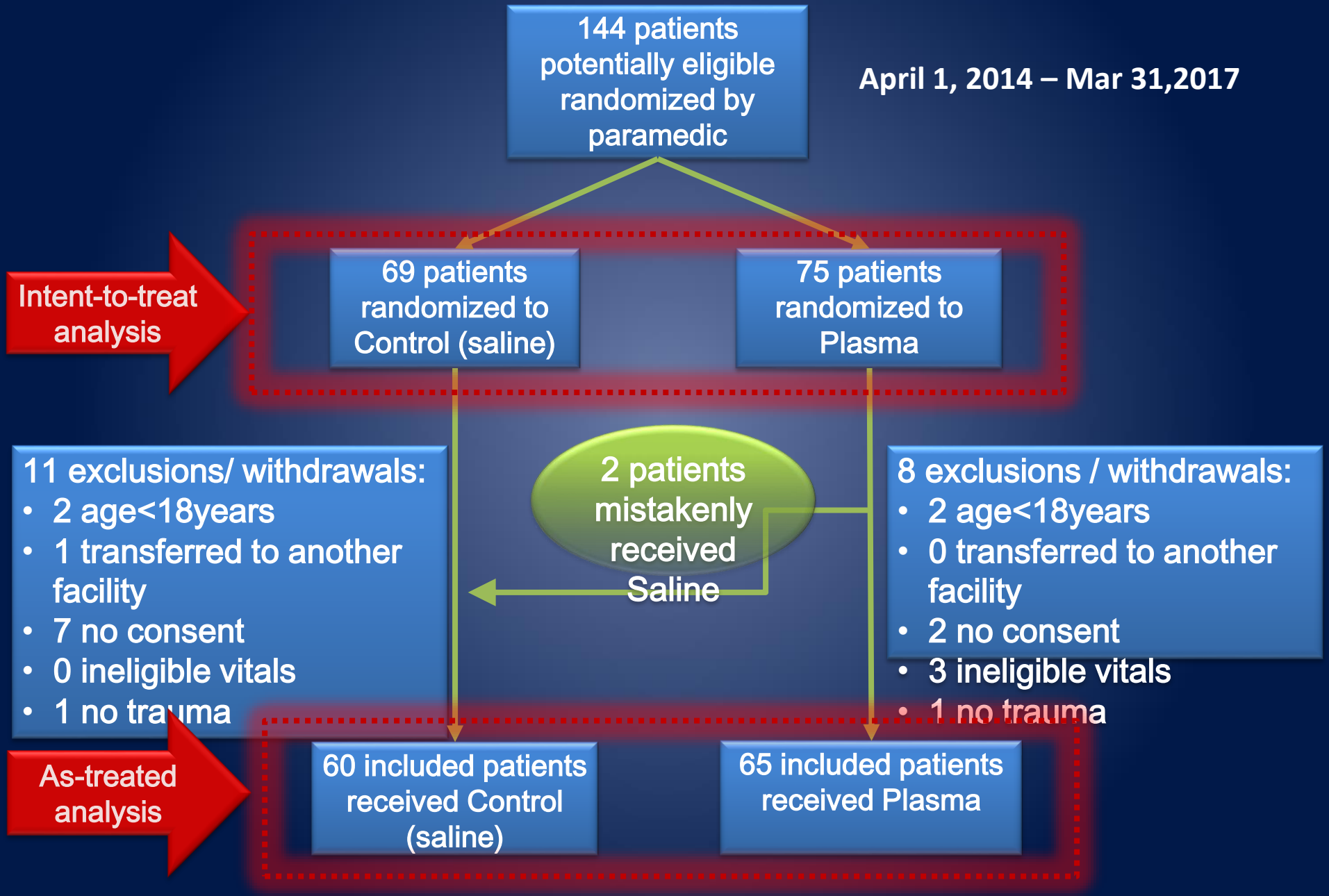
Megan Swope

Josh Ryon

Stephanie Jarvis

Sam McGuffin

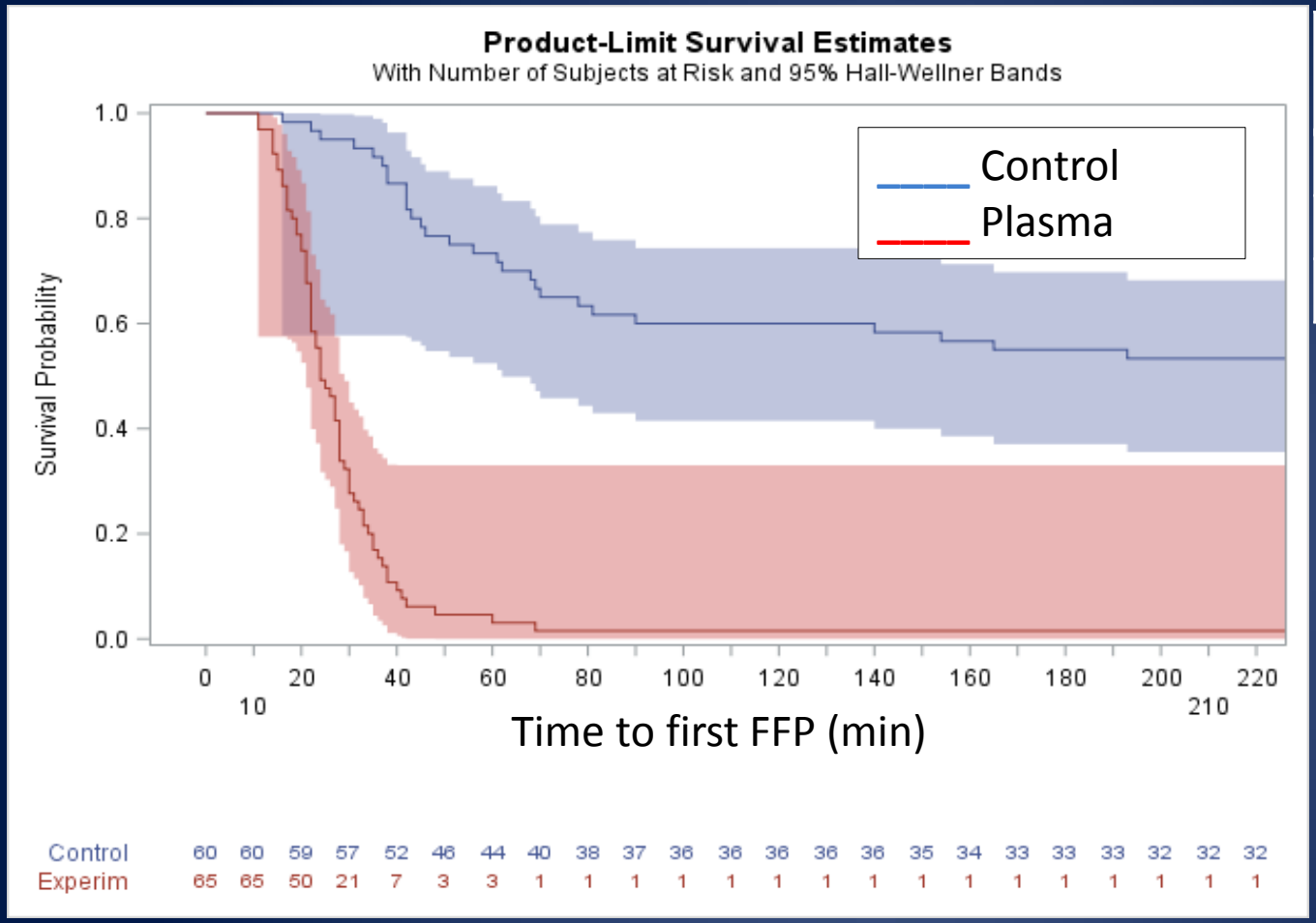
COMBAT Study



Effectiveness of Randomization

Injury related variables	Control	Plasma
	% or Median (IQR)	% or Median (IQR)
PHYSIOLOGY/SHOCK		
Worst HR	112 (100-120)	110 (98-120)
Worst SBP	**70 (55-80)**	**64 (50-80)**
Severe shock (SBP<=70mmHg)	55%	68%
Worst Temp	36 (35.1-37)	36 (34.8-36.6)
Worst GCS	14 (8-15)	14 (7-15)
Hgb	**14.2 (13.1-16)**	**15.1 (13.5-15.7)**
Platelet Count (1000)	**273.5 (218-336)**	**300.5 (250-357)**
Fibrinogen	**278 (250-331)**	**253 (224-310)**

Time from injury to 1st Plasma

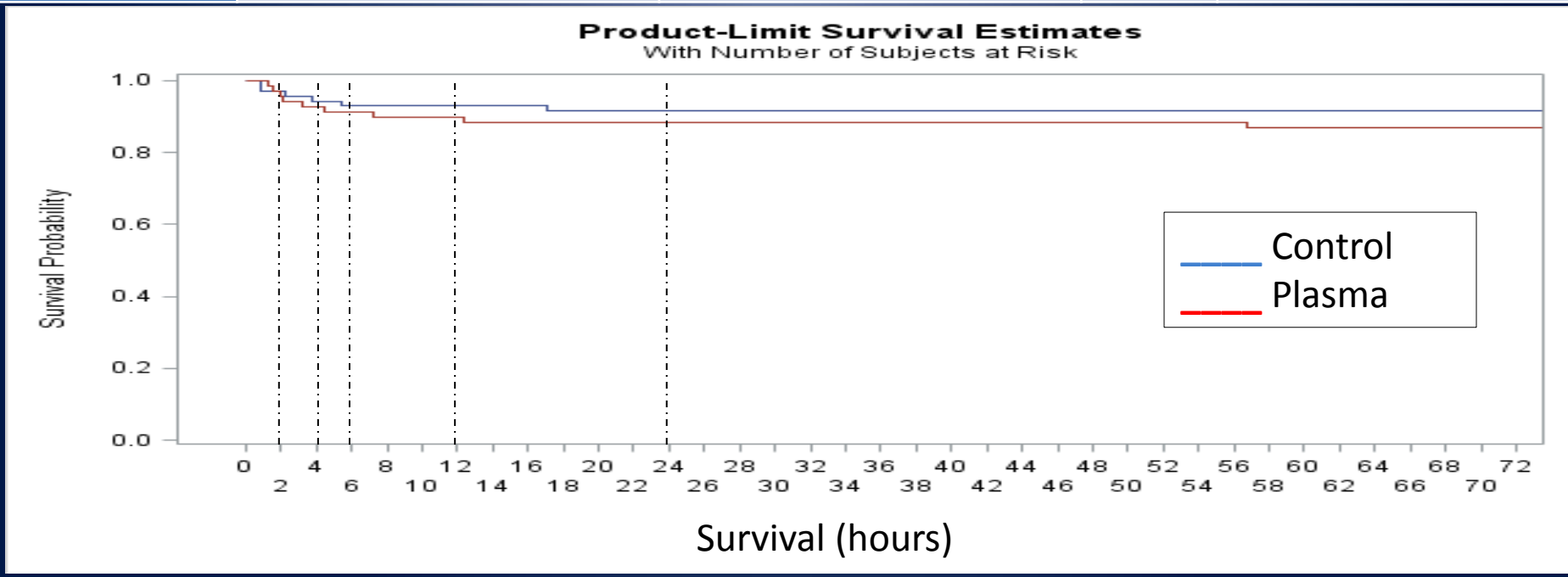


Test of Equality over Strata	
Test	P-value
Wilcoxon	<.0001
Log-Rank	<.0001

Conclusion: by design, Plasma group patients received plasma earlier (~ 30 minutes before) than Controls.

Primary Endpoints

Primary Endpoints	Control N=60	Plasma N=65	P-value	Expected %
28-day Mortality	**3 (5%) potentially preventable** 3 (5%) non-preventable	**4 (6%) potentially preventable** 6 (9%) non-preventable	0.37	**ROC trial (2006-08): 25%** MTP trial (2011-14): 20% PROPHET (2010-11): 18%
28-day MOF	**1 (2%)**	**4 (6%)**	0.37	Glue Grant: 10%
Death or MOF (composite)	7 (12%)	14 (21%)	0.14	Glue grant: 16%



Secondary Endpoints

Secondary endpoints	Control N=60	Plasma N=65	
Variable	Median (IQR) or %	Median (IQR) or %	p-value
Arrival INR	1.15 (1.08-1.29)	1.27 (1.11-1.40)	0.10
INR >1.3	24%	43%	0.0298
BD >8 mEq/L	52%	55%	0.77
Lactate >5mmol/L	48%	51%	0.77
Hyperfibrinolysis (>3%)	25%	24%	
Physiologic (0.9-3%)	45%	44%	0.93
Shutdown (<0.9%)	29%	33%	

COMBAT Conclusions

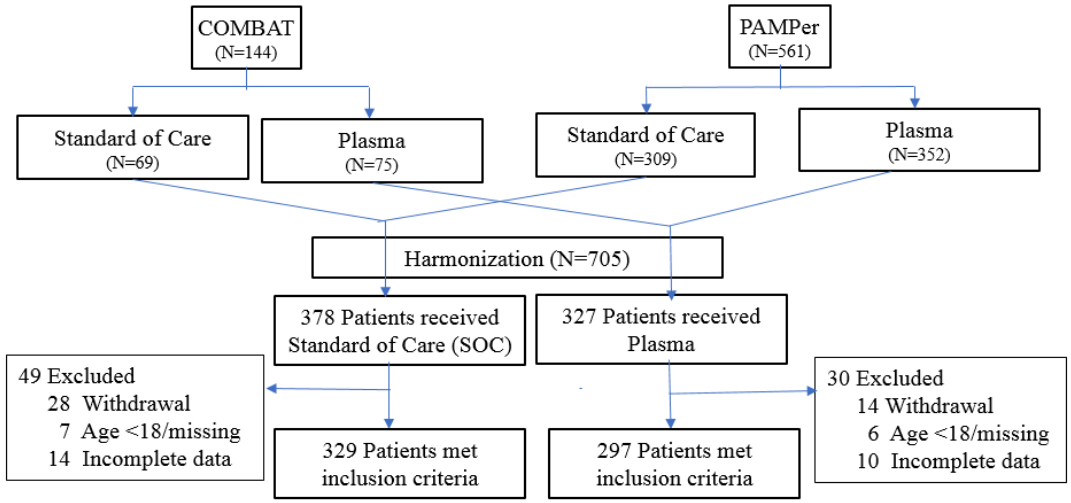
In a mature urban trauma system with rapid transport to a level I trauma center ….

pre-hospital plasma does not improve outcome

PREHOSPITAL PLASMA IMPROVES SURVIVAL IN TRAUMA PATIENTS WITH HEMORRHAGIC SHOCK WHEN TRANSPORT TIMES ARE LONGER THAN 20 MINUTES

Anthony E. Pusateri, PhD[1]; Ernest E. Moore, MD[2]; Hunter B. Moore, MD, PhD[2]; Tuan D. Le, MD, DrPH[1]; Francis X. Guyette, MD, MPH[3]; Michael P. Chapman, MD[4]; Angela Sauaia, MD, PhD[5]; Arsen Ghasabyan, MPH[2]; James Chandler[2]; Kevin McVaney, MD[6]; Joshua B. Brown, MD[7]; Brian J. Daley, MD[8]; Richard S. Miller, MD[9]; Brian G. Harbrecht, MD[10]; Jeffrey A. Claridge, MD[11]; Herb A. Phelan, MD, MSCS[12]; William R. Witham, MD[13]; A. Tyler Putnam, MD[14]; Jason L. Sperry, MD, MPH[7]

PAMPer & COMBAT



Same populations (n=626) included in original two published studies

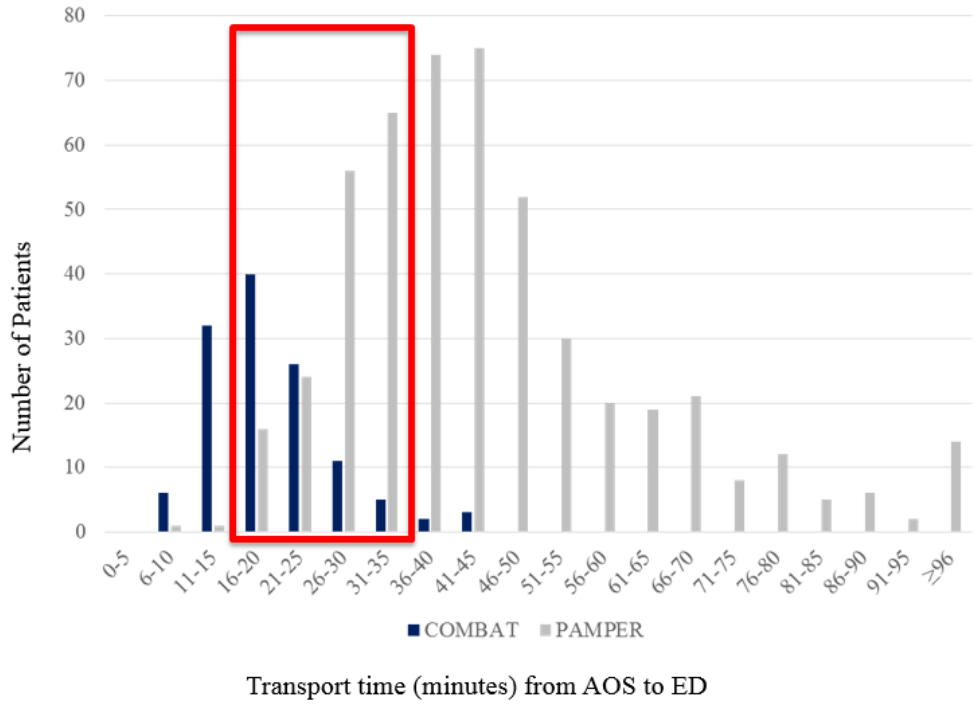
JAMA Surg In Press

Demographics (1/2)

	All	SC	Plasma	P Value
Number of participants, No. (%)	626 (100)	329 (52.6)	297 (47.4)	
Cohort, No. (%) COMBAT	125 (20.0)	58 (17.6)	67 (22.6)	0.12
PAMPer	501 (80.0)	271 (82.4)	230 (77.4)	
Male sex, No. (%)	467 (74.6)	251 (76.3)	216 (72.7)	0.31
Median age (IQR), y	42 (27-57)	42 (26-57)	43 (29-56)	0.67
Race/Ethnicity, No. (%)				0.26
White	453 (72.4)	239 (72.6)	214 (72.1)	
Black	69 (11.0)	40 (12.2)	29 (9.8)	
Hispanic	64 (10.2)	27 (8.2)	37 (12.5)	
Other/ Unknown	40 (6.4)	23 (7.0)	17 (5.7)	
Mechanism of injury, No. (%)				0.51
Fall	38 (6.1)	23 (7.0)	15 (5.1)	
MVC (Motorcyclist/cyclist and occupant)	338 (54.0)	185 (56.2)	153 (51.2)	
MVC (Pedestrian or struck by or against)	57 (9.1)	29 (8.8)	28 (9.4)	
Firearm	77 (12.3)	35 (10.6)	42 (14.1)	
Stab wound	69 (11.0)	32 (9.7)	37 (12.5)	
Other	47 (7.5)	25 (7.6)	22 (7.4)	
Type of injury, No. (%) (10 pts count for both)				0.37
Blunt	475 (74.7)	257 (78.1)	218 (73.4)	
Penetrating	161 (25.3)	77 (23.4)	84 (28.3)	

Harmonized Data – Transport Time

Distribution of Prehospital Transport Times



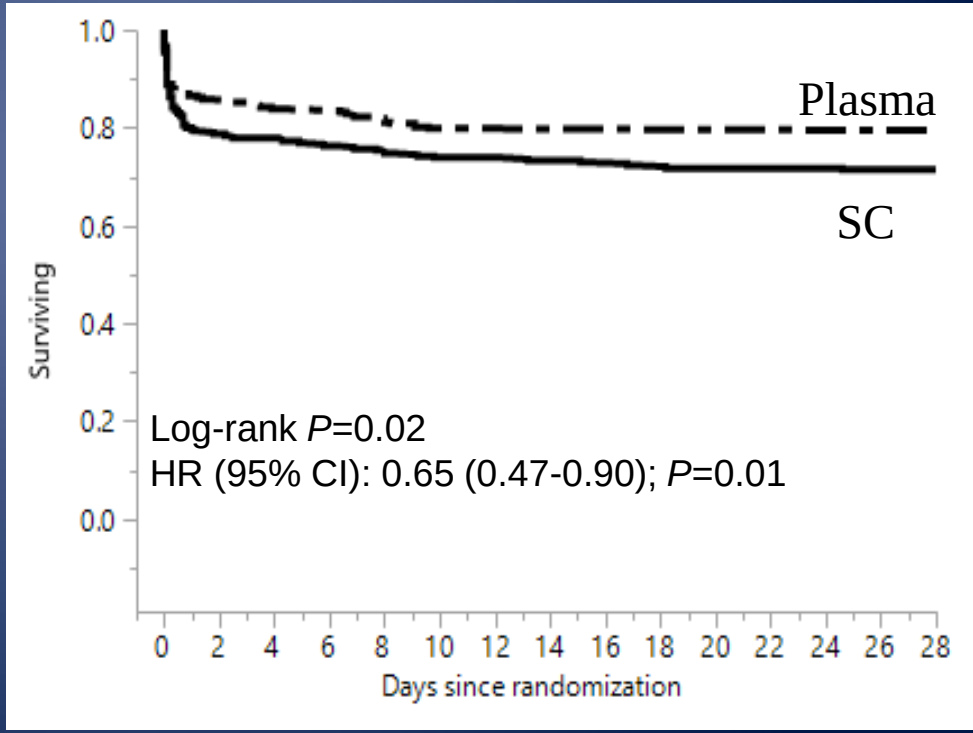
Median prehospital transport time was longer in the PAMPer study compared to COMBAT, 41 minutes vs. 18 minutes; $P<.001$, but there was overlap between the two studies

Prehospital Plasma Reduced Mortality

Mortality

	SC	Plasma	P
28 d	94 (28.6)	61 (20.5)	0.02
24 h	67 (20.4)	40 (13.5)	0.02

Plasma vs Saline Control



Conclusion:

- **Prehospital Plasma Improves Survival with Transport Time > 20 min**

- **Impact of Prehospital Blood Products Depends on the Environment**

Thank you !!!

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