ORBCoN
Ontario Regional Blood Coordinating Network

Inspiring and facilitating best transfusion practices in Ontario.

FiiRST-2 Trial – Factors in the Initial Resuscitation of Severe Trauma

A 2020 EAST Multicenter Trial

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Disclosure

- Support for research and honoraria from Octapharma AG
- Support for research from the Defense Research and Development Canada (DRDC)
- Support for research from the Canadian Institutes for Health Research (CIHR)

Why investigate pre-emptive use of clotting factors concentrates (CFCs) as an alternative to plasma in bleeding trauma patients?

Literature assessing optimal hemostatic resuscitation

Randomized controlled trials

		Findings			Bottom line	
	Intervention	Primary outcome	Primary outcome	Secondary outcomes	Efficacy	Safety
RETIC **LANCET Jun 2017**	FC + PCC vs. plasma (n=100)	MOF assessed by SOFA score	No difference in MOF but trial stopped for futility	↑ rescue therapy with FC and ↑ massive transfusion with plasma	**FC + PCC** ↓ massive transfusion	No difference in TE events
PROCOAG **JAMA Mar 2023**	Plasma + PCC vs. plasma (n=324)	24-h all blood product consumption	No Difference in consumption	↑ risk of TE complications	**Plasma + PCC** Same blood consumption	↑ in TE events
CRYOSTAT-2 **JAMA Oct 2023**	Plasma + cryo vs. plasma (n=1604)	28-day all-cause mortality	No difference in mortality	No difference in TE complications	**Plasma + cryo** No difference in 28-day all-cause mortality	No difference in TE events

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- **Further contribution from the iTACTIC trial?**
  - Multicenter RCT
  - Intervention: VET vs. CCTs guided hemostatic interventions on top of MHP 1:1:1
  - **VET 61 min** vs. CCT 80 min

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  - Multicenter RCT
  - Intervention: VET vs. CCTs guided hemostatic interventions on top of MHP 1:1:1
  - **VET 61 min** vs. CCT 80 min

Possible benefits of clotting factor concentrates approach:

- Easier logistics – bedside storage at room temperature
- Faster administration
- Pathogen-reduced
- No need for ABO matching
- Smaller volume per dose

- **FiiRST-2 Design:**
  Multicenter, randomized, parallel-control (active), single-blinded (outcome accessors), **superiority trial** at 6 Level 1 Trauma Centers, across Canada, with an **adaptive interim analysis**.
- **Sample size (n=350):**
  Clinically meaningful difference: 5 units (plasma 15 vs. FC+PCC 10), 80% power. **Planned interim analysis** for power and sample size re-estimation after 120 patients enrolled, consented, and treated.
- **Stopping rule – power 25% or less.**

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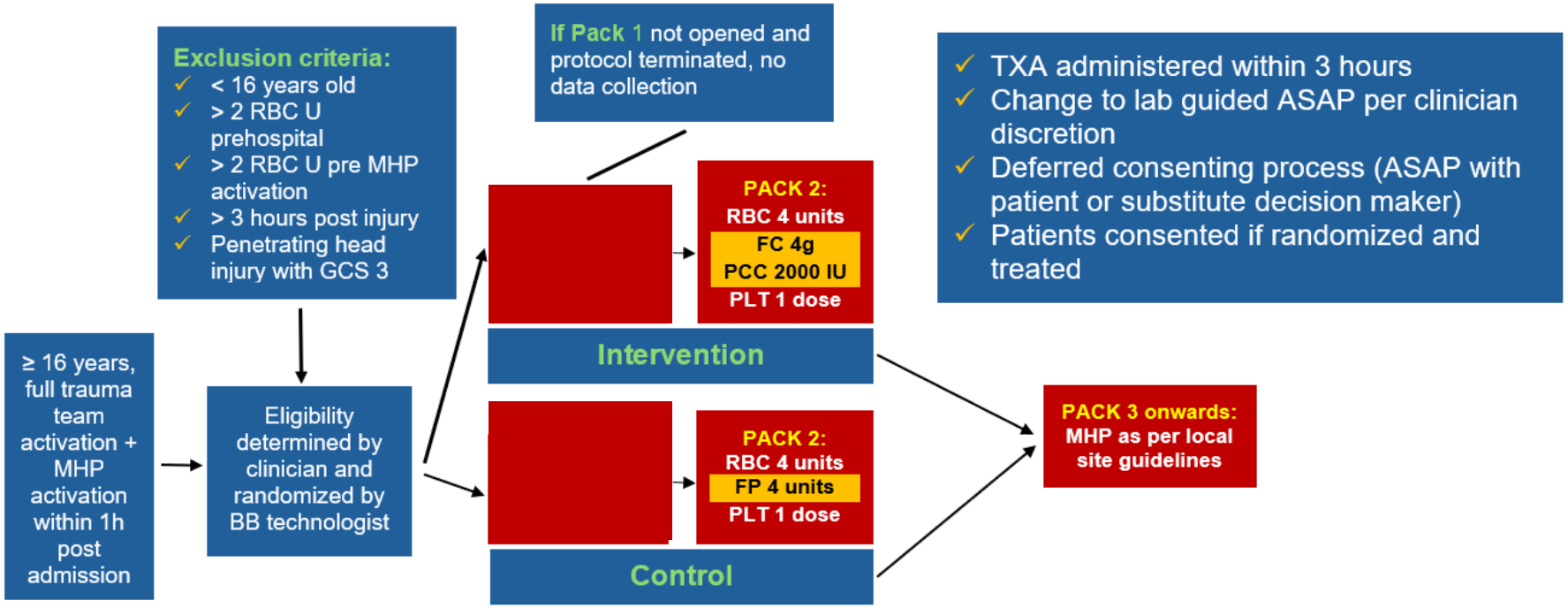
- **Primary analysis (modified ITT population):** all randomized patients who **received any of the products in pack 1 or beyond, consented,** and **remained** in the study

FiiRST-2 Procedures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✓ > 2 RBC U pre MHP activation
✓ > 3 hours post injury
✓ Penetrating head injury with GCS 3
If Pack 1 not opened and protocol terminated, no data collection
✓ TXA administered within 3 hours
✓ Change to lab guided ASAP per clinician discretion
✓ Deferred consenting process (ASAP with patient or substitute decision maker)
✓ Patients consented if randomized and treated
≥ 16 years, full trauma team activation + MHP activation within 1h post admission
Eligibility determined by clinician and randomized by BB technologist
PACK 2:
RBC 4 units
FC 4g
PCC 2000 IU
PLT 1 dose
Intervention
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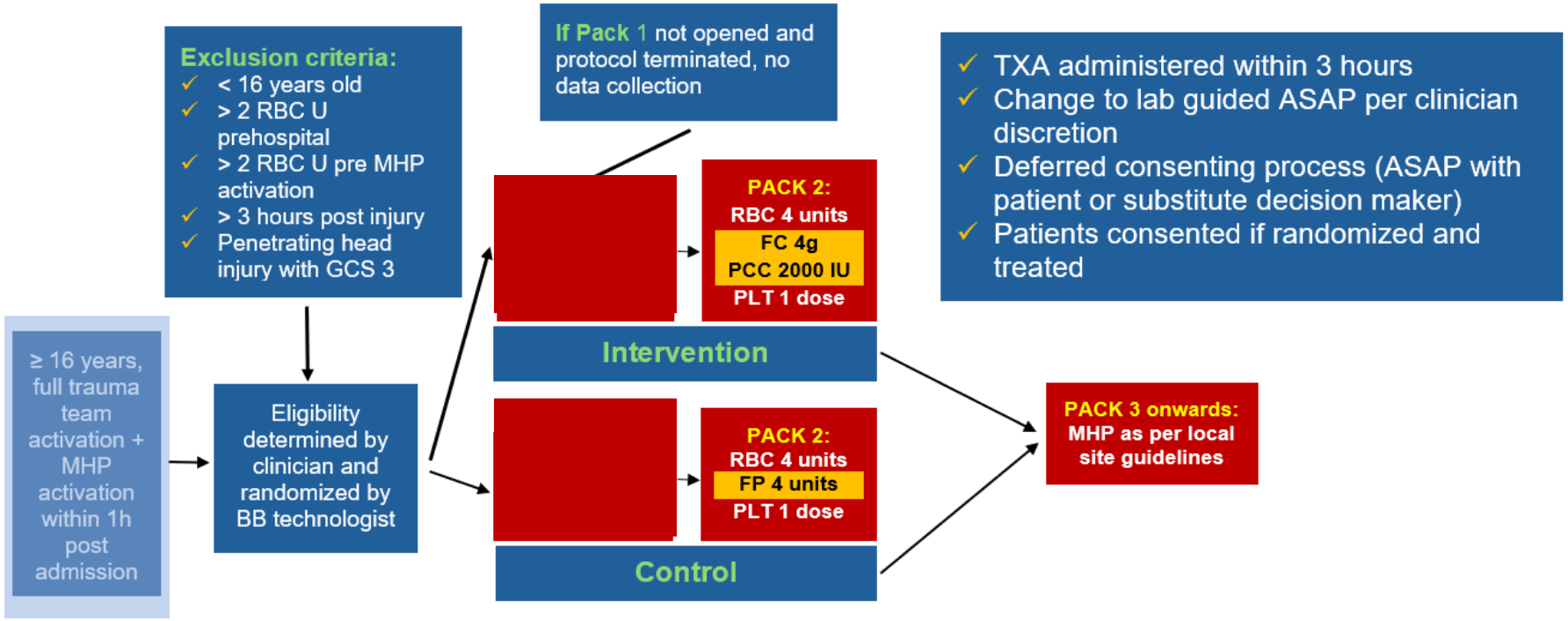
FP 4 units
PLT 1 dose
Control
PACK 3 onwards:
MHP as per local site guidelines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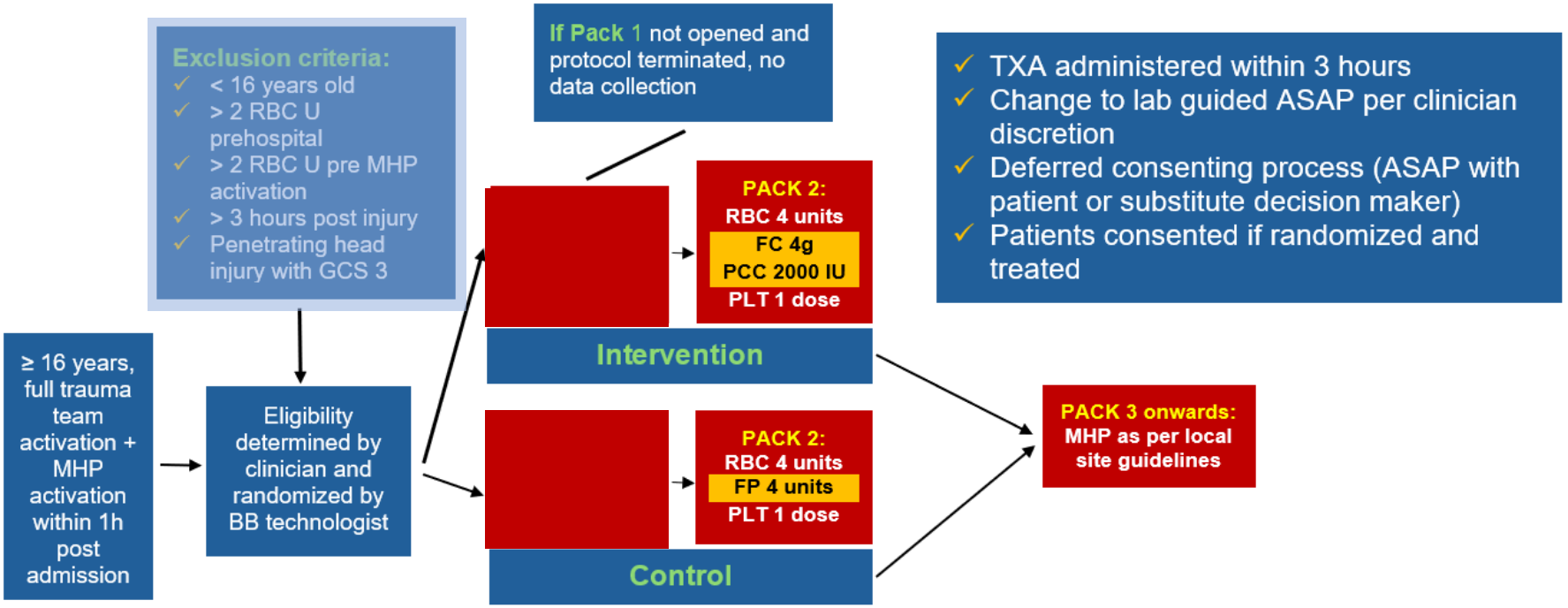
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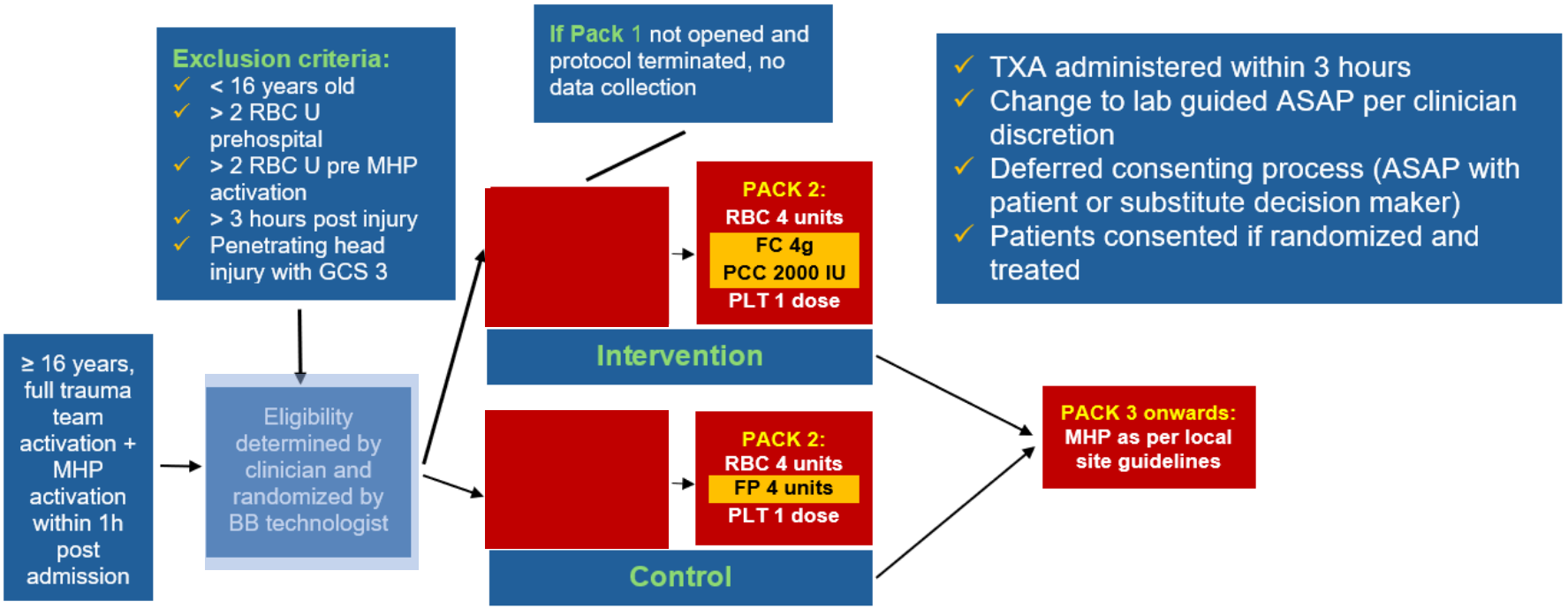
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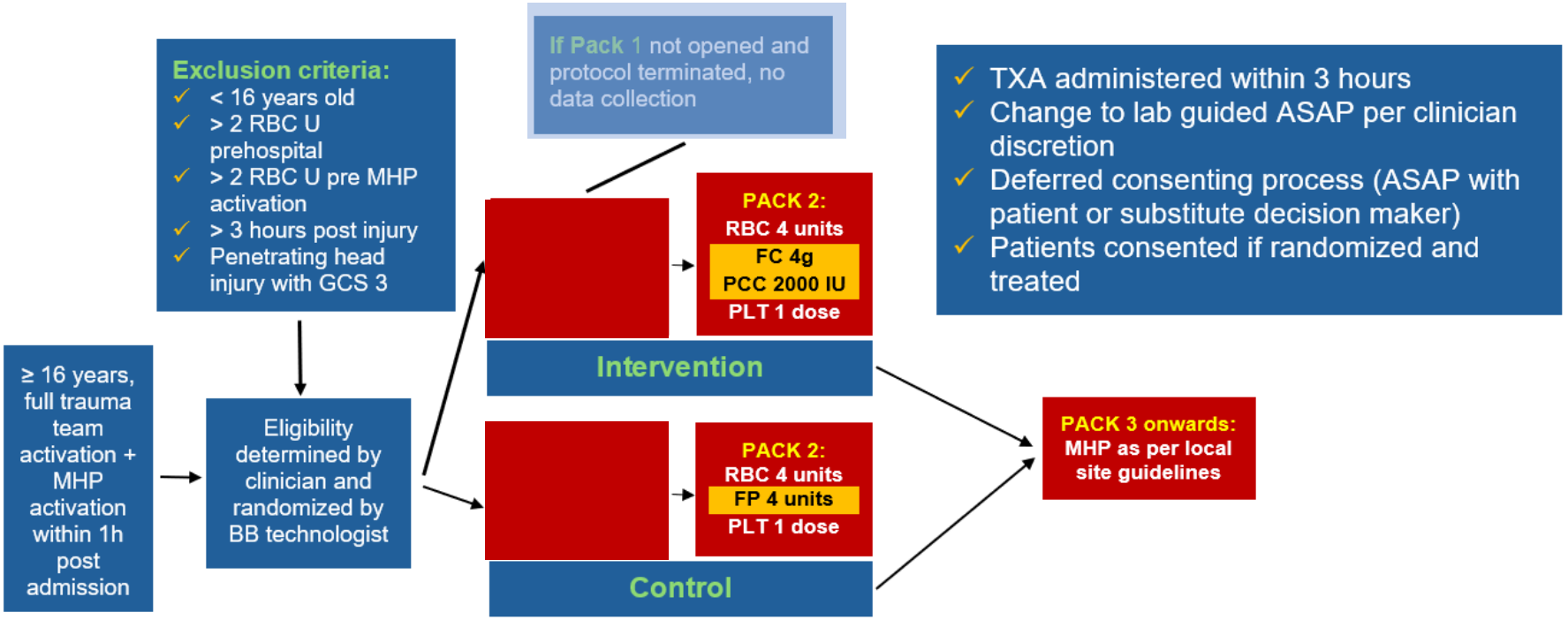
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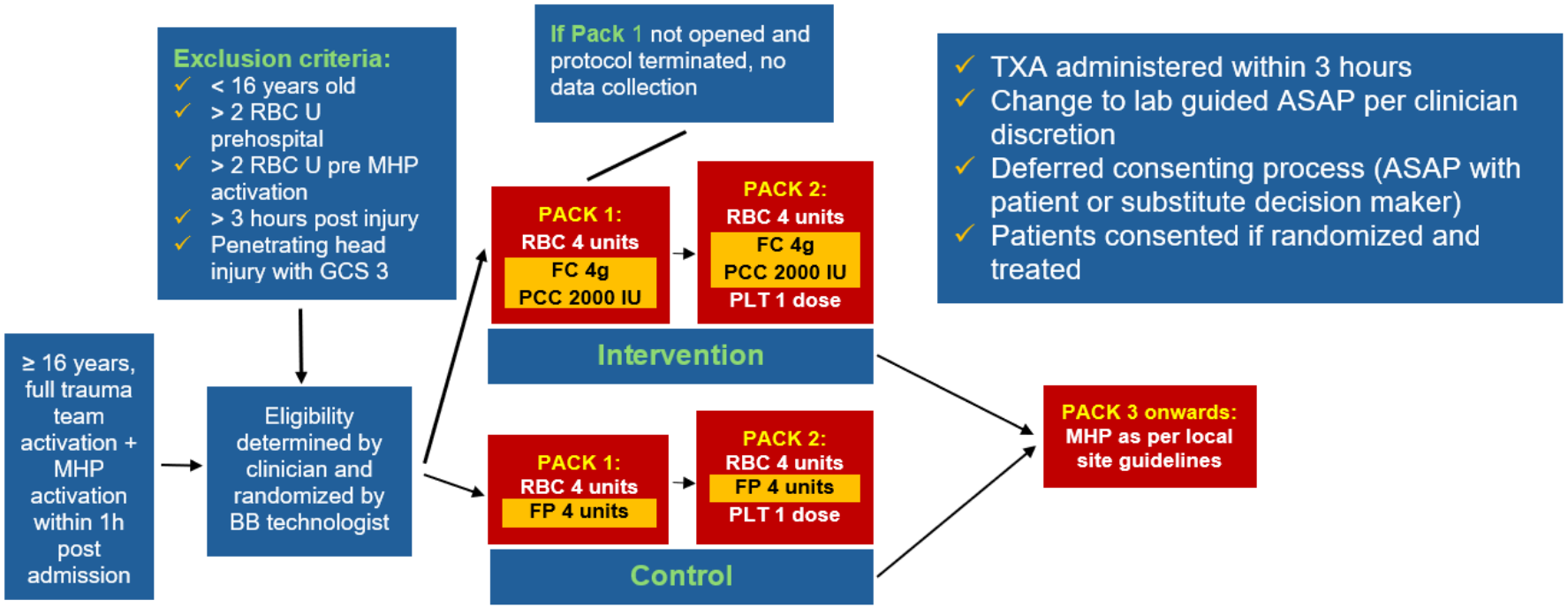
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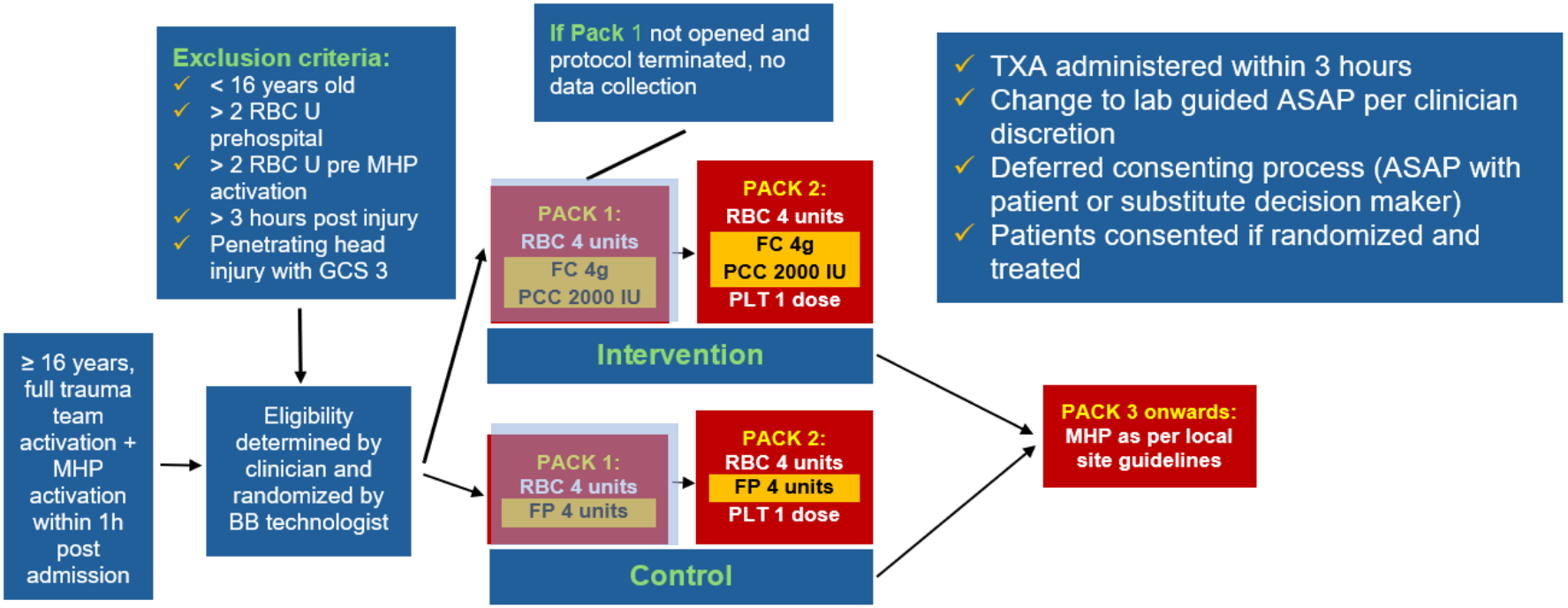
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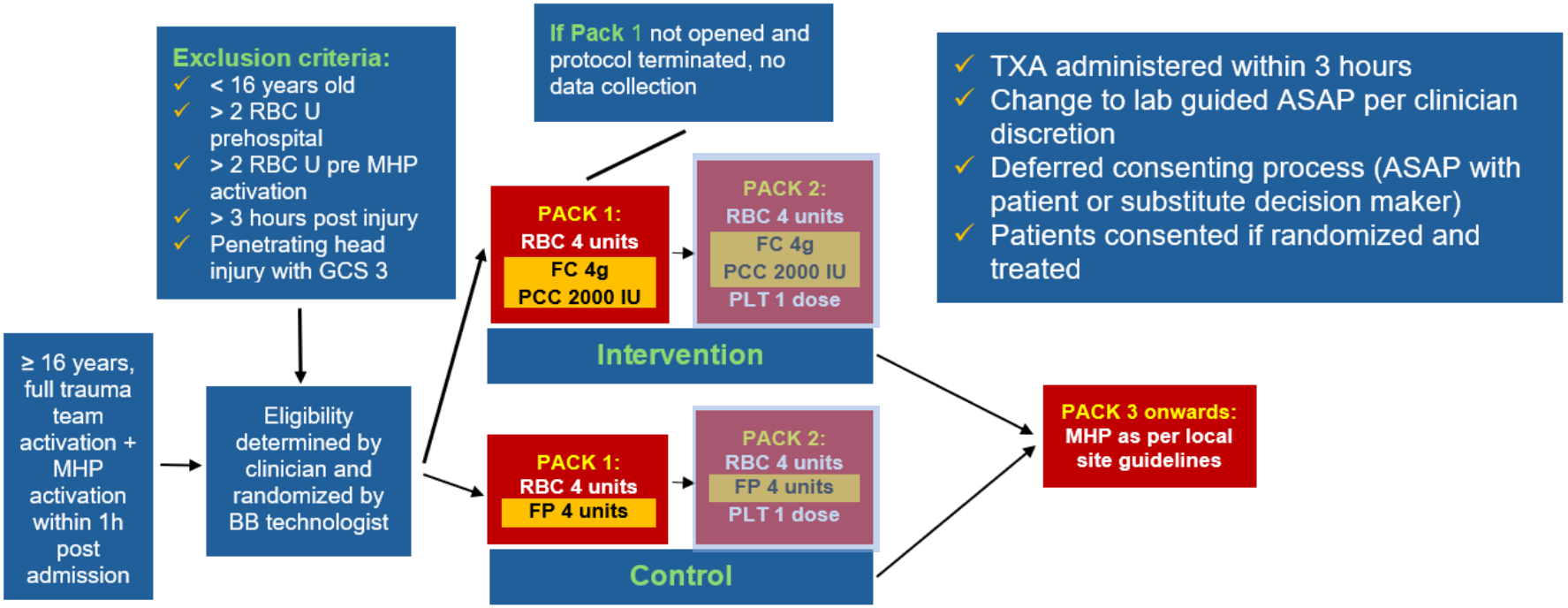
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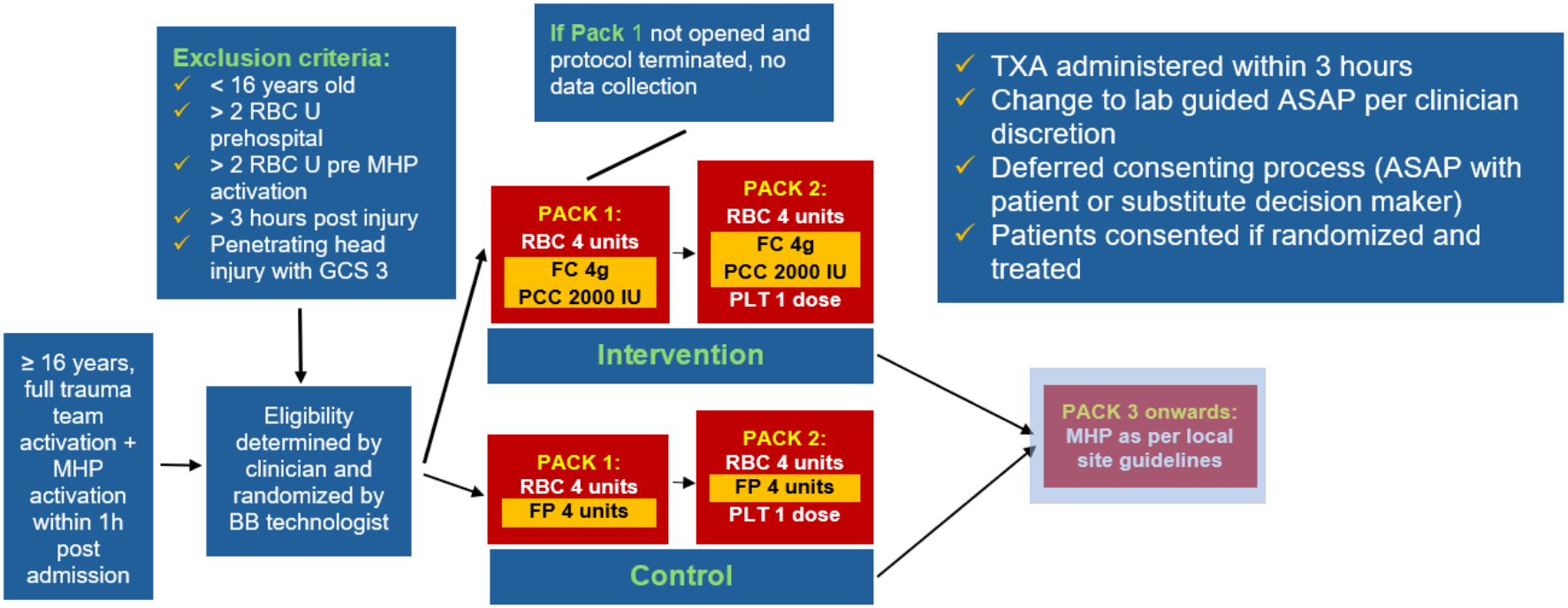
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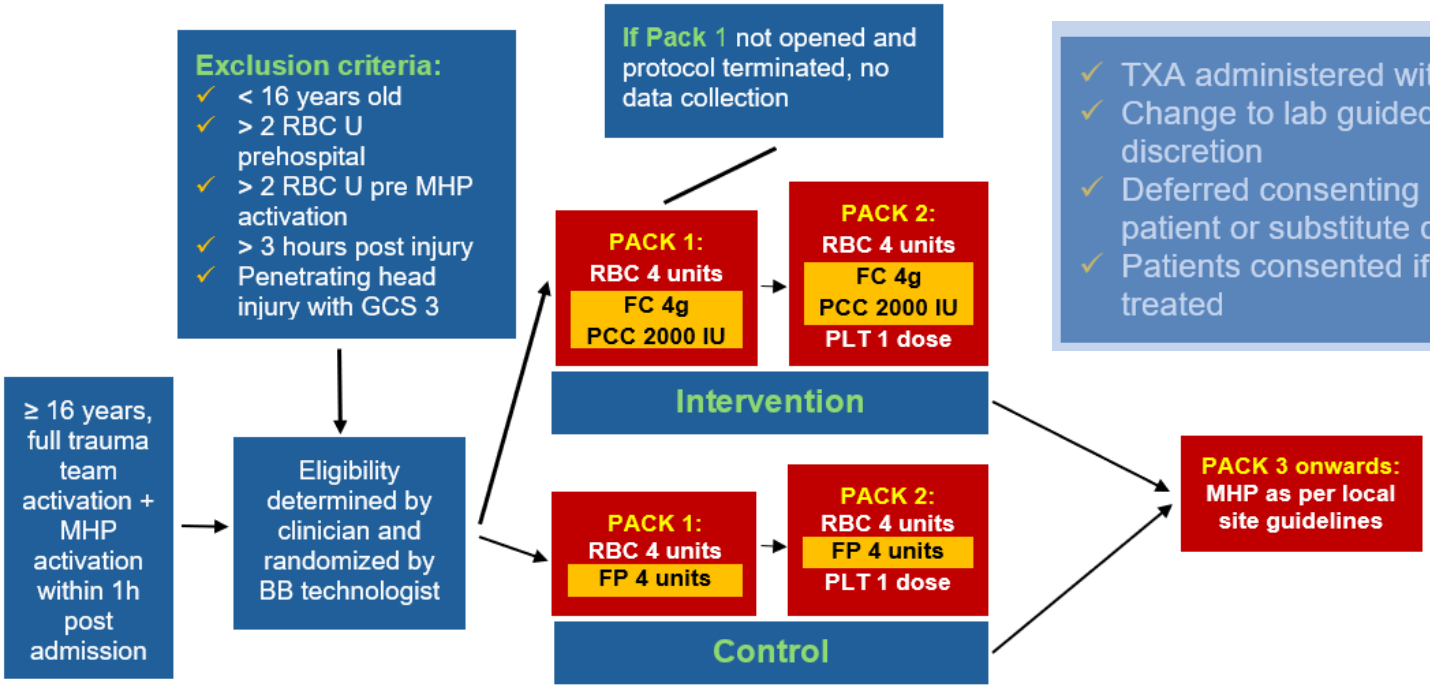
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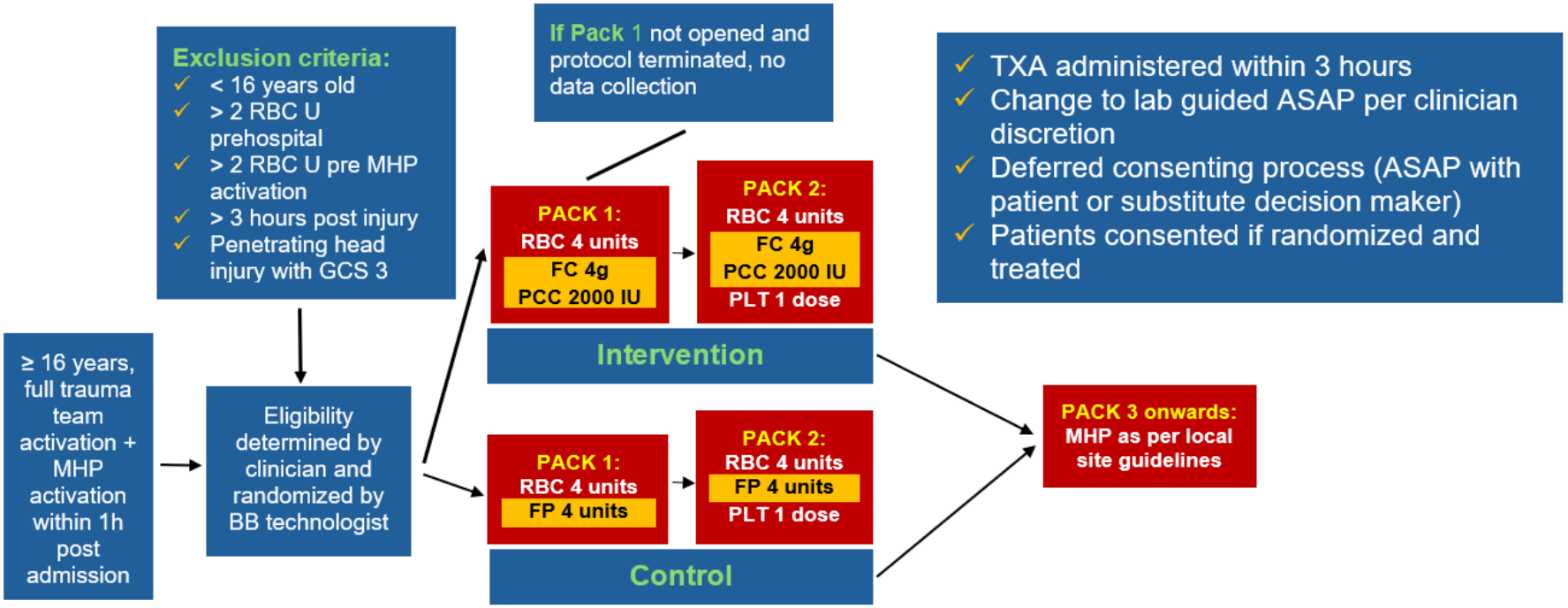
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- **Objective:** to assess **efficacy and safety of** CFCs as **compared to plasma**

Primary outcome:

Units of RBC + plasma + platelets transfused within 24 hours

Secondary outcome:

Units of RBC + plasma + platelets transfused within 24 hours **without the active control** (up to 8 plasma units)

Secondary outcomes (efficacy)

- **Transfusion**
  - Units of RBC ≤ 24 h (surrogate for hemorrhage control)
  - Individual units of RBC, plasma, platelets ≤ 24 h
  - Volume of crystalloids / colloids volume ≤ 24 h
  - Use of hemostatic interventions (FC, PCC, FVIIa, FXIII) ≤ 24 h
- **Clinical**
  - Ventilator-free days
  - Duration of ICU stay
  - Days out of hospital within 28 days
  - 24-hour mortality
  - 28-day all-cause mortality
- **Laboratory tests**

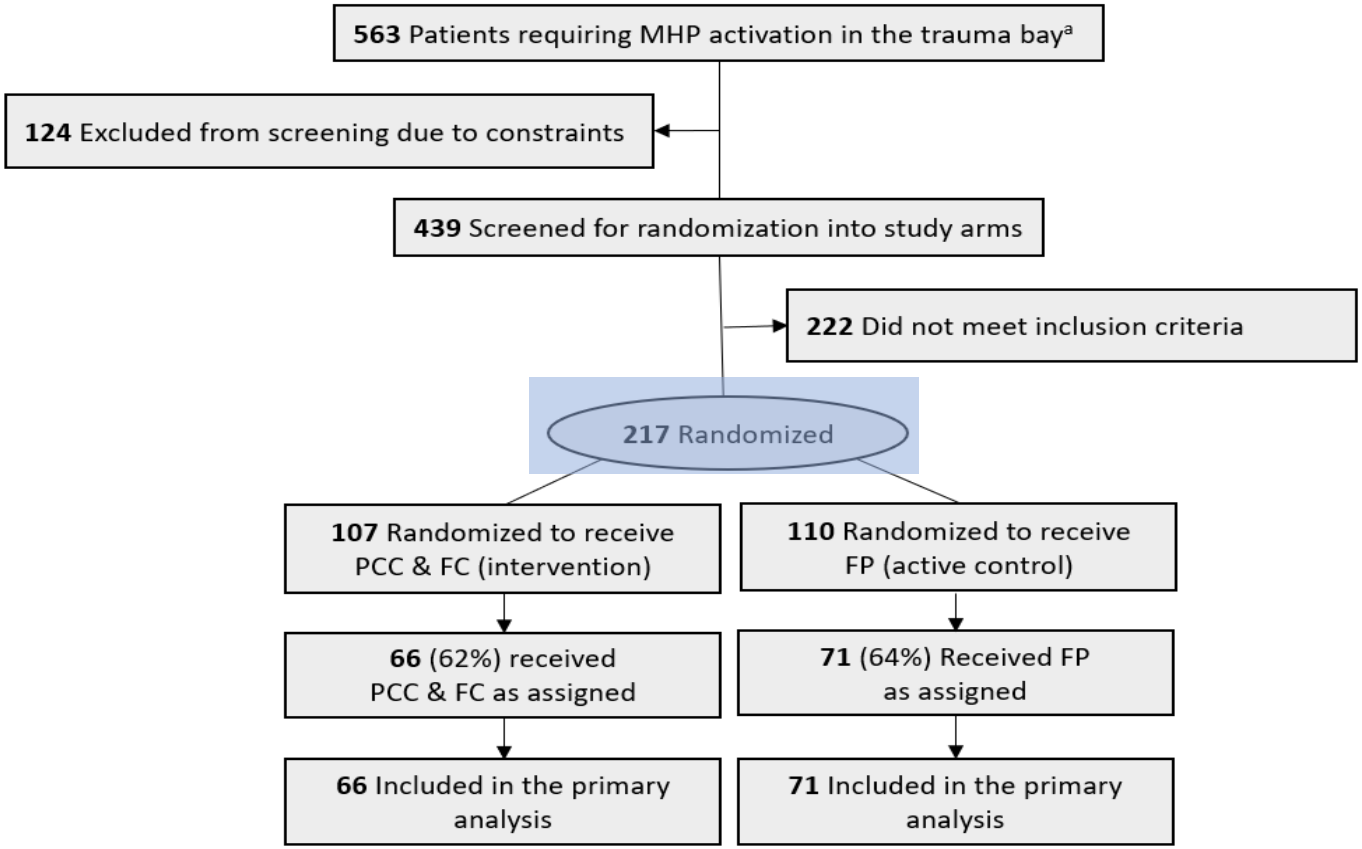
Secondary outcomes (safety)

Clinical:

- Multiorgan failure
- Abdominal compartment syndrome
- Limb compartment syndrome
- Transfusion reactions
- Treatment-emergent adverse events
  - CVA, MI, DVP, PE, other TE events

FiiRST-2 Results

FiiRST-2 CONSORT diagram



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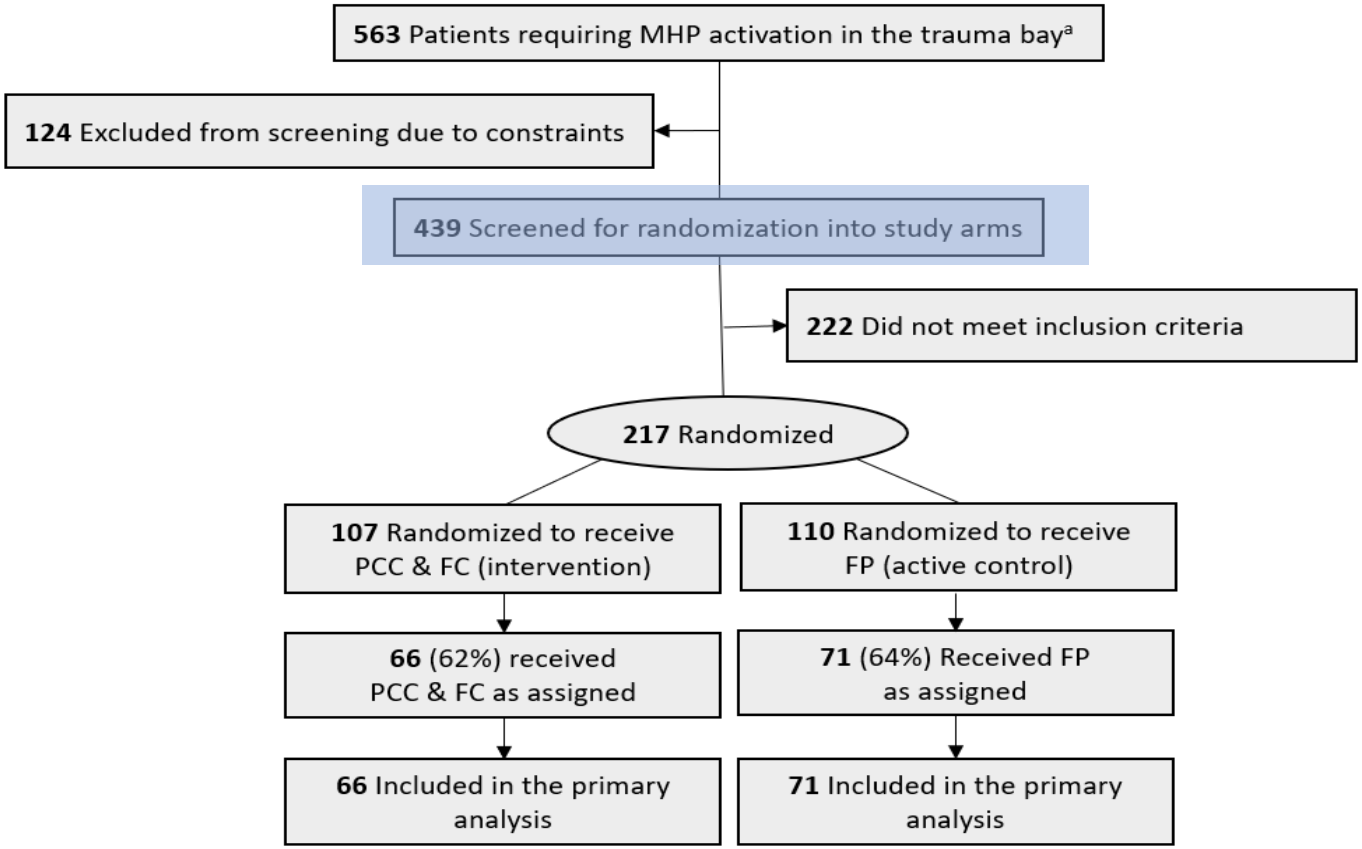

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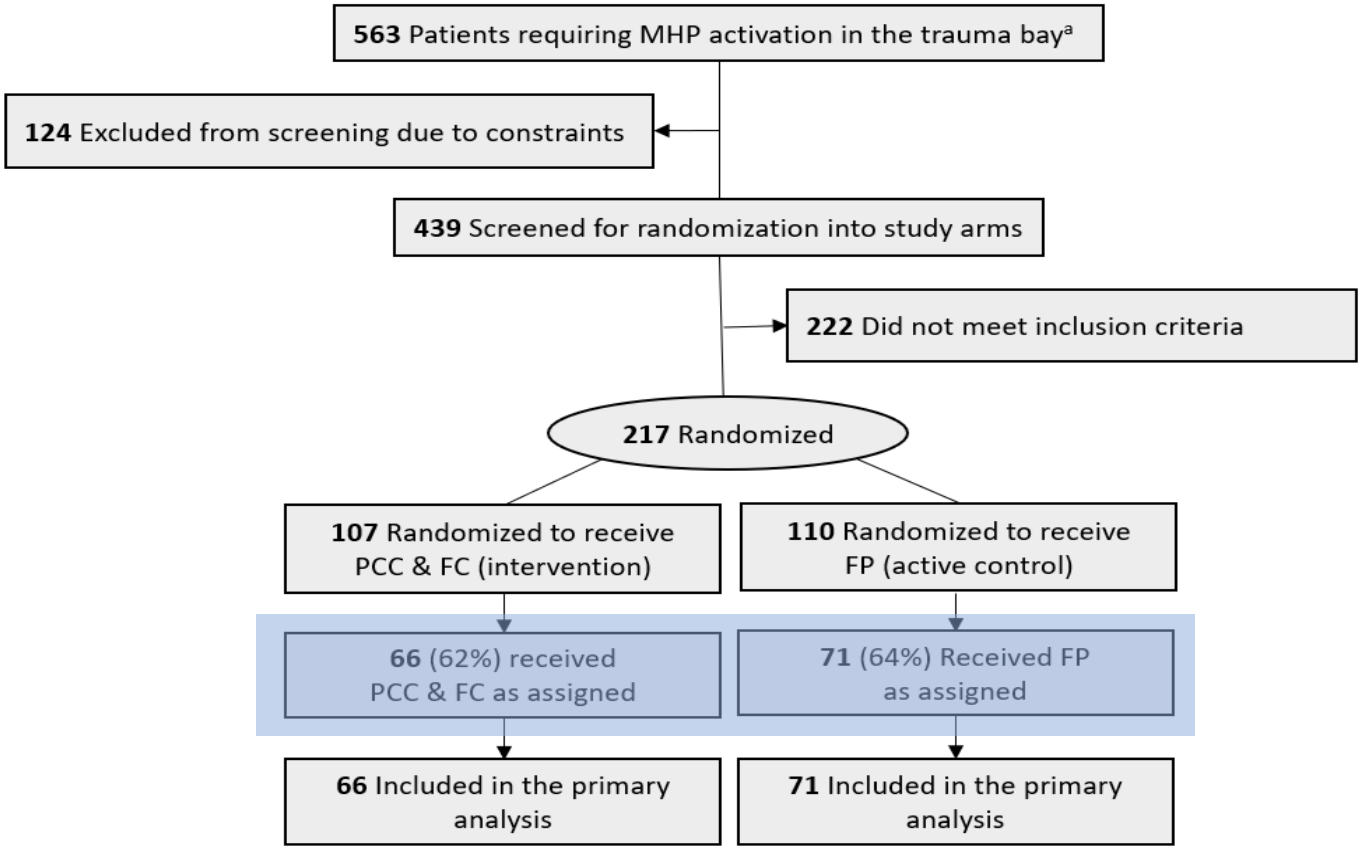

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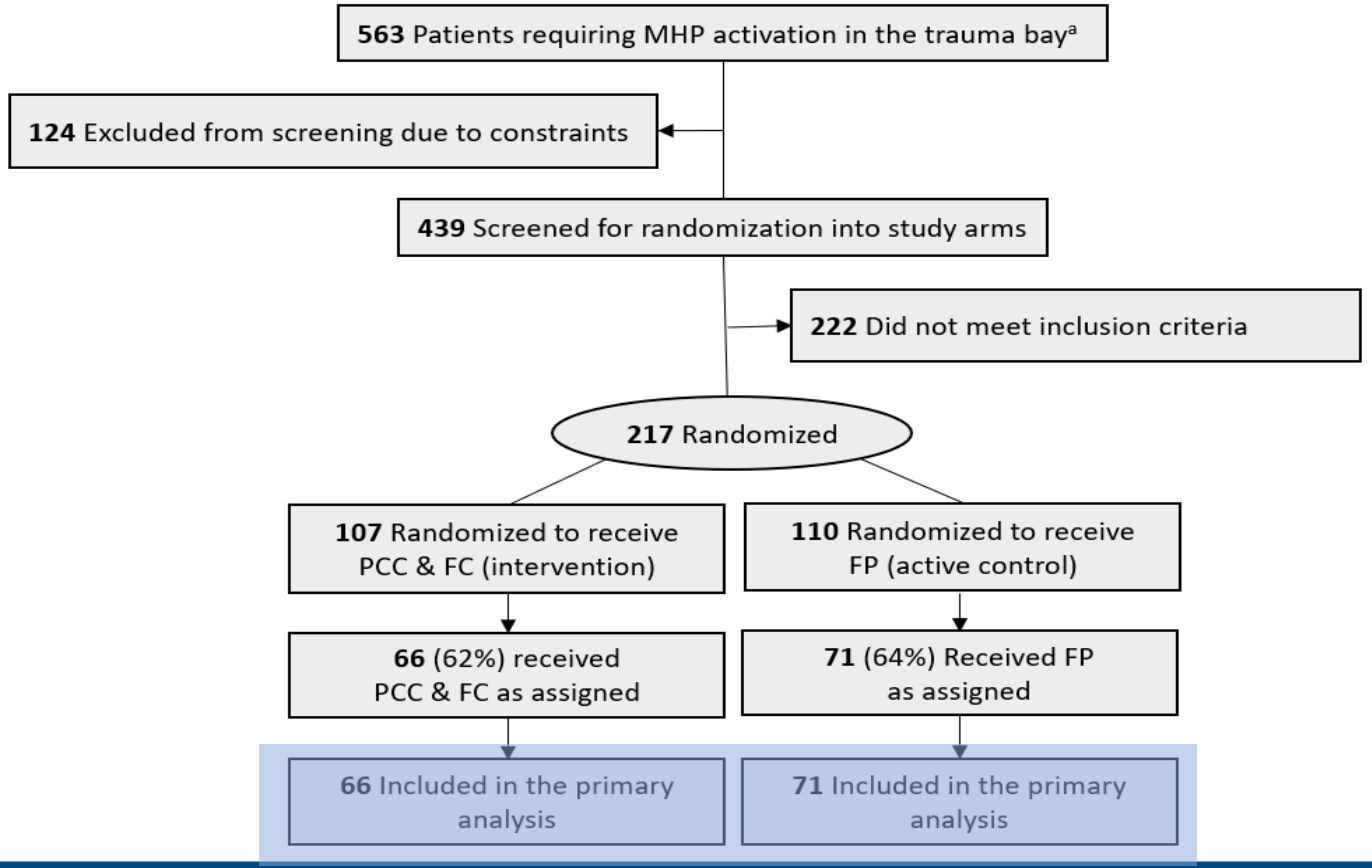

FiiRST-2 Demographics

Characteristic	Treatment Group		All patients (n = 137)
	Plasma (n = 71)	FC and PCC (n = 66)	
Demographics			
Age (years), median (IQR)	41 (31, 55) [n=69]	35 (27, 53)	38 (29, 55) [n=135]
Female, No. (%)	15 (21)	11 (17)	26 (19)
Male, No. (%)	56 (79)	55 (83)	111 (81)
BMI (kg/m^2), median (IQR)	27 (23, 32) [n=51]	27 (24, 29) [n=44]	27 (23, 31) [n=95]

Characteristic	Treatment Group		All patients (n = 137)
	Plasma (n = 71)	FC and PCC (n = 66)	
Injury data			
Mechanism			
Blunt, No. (%)	47 (66)	48 (73)	95 (67)
Penetrating, No. (%)	25 (35)	21 (32)	46 (33)
Injury severity			
ISS (points), median (IQR)[a]	29 (22, 43) [n=70]	33 (18, 45)	29 (19, 43) [n=136]
ISS ≥15, No. (%)	63 (89)	54 (82)	117 (85)
AIS Head score ≥ 3 No. (%)[b]	19 (27) [n=70]	22 (33)	41 (30) [n=136]
GCS (points), median (IQR)[c]	10 (3, 15)	14 (5, 15)	13 (5, 15)
Severe (Score (0-8)	30 (42)	20 (30)	50 (36)

Characteristic	Treatment Group		All patients (n = 137)
	Plasma (n = 71)	FC and PCC (n = 66)	
Physiologic data on admission			
HR /min			
median (IQR)	111 (88, 129) [n=68]	113 (95, 134) [n=64]	113 (92, 131) [n=132]
>120 /min, No. (%)	28 (39) [n=68]	27 (41) [n=64]	55 (40) [n=132]
Systolic BP (mmHg)			
median (IQR)	127 (85, 152) [n=65]	108 (93, 138) [n=61]	114 (89, 148) [n=126]
≤ 90 mmHg, No. (%)	20 (28)	14 (21)	34 (25)
ABC score ≥ 2 (points), No. (%)[d]	35 (49)	28 (42)	63 (46)
Shock Index > 1.0, No. (%)[e]	25 (35)	29 (44)	54 (39)

Characteristic	Treatment Group		All patients (n = 137)
	Plasma (n = 71)	FC and PCC (n = 66)	
Laboratory data on admission			
Blood pH, median (IQR)[f]	7.2 (7.2, 7.3)	7.2 (7.2, 7.3)	7.2 (7.2, 7.3)
Base deficit (mmol/L), median (IQR)[f]	8 (4, 11)	8 (4, 10)	8 (4, 11)
Lactate (mmol/L), median (IQR)[f]	5 (4, 7)	5 (4, 8)	5 (4, 7)
Haemoglobin (mg/dL), median (IQR)[f]	116 (102, 133)	121 (111, 131)	121 (107, 133)
INR, median (IQR)[g]	1.3 (1.2, 1.6)	1.3 (1.2, 1.5)	1.3 (1.2, 1.5)
INR > 1.2, No. (%)	37 (52)	36 (54)	73 (53)
INR > 1.5, No. (%)	13 (18)	11 (17)	24 (17)
Fibrinogen (g/L), median (IQR)[f]	1.7 (1.2, 2.4)	1.9 (1.4, 2.4)	1.8 (1.3, 2.4)
Fibrinogen ≤ 1.5 (g/L), No. (%)	17 (24)	12 (18)	29 (21)
Platelets (× 10^9/L), median (IQR)[f]	220 (149, 226)	208 (162, 263)	215 (155, 270)

Resuscitation indicators

Characteristic	Treatment Group		All patients (n=137)
	Plasma (n=71)	FC and PCC (n=66)	
Transfusion of ≥3 RBCU of RBCs within the first hour, No. %	60 (84.5)	52 (78.8)	112 (81.8)
Tranexamic acid infused, No. (%)	64 (90.1)	59 (89.4)	123 (89.8)
Time from injury to TB/ED (minutes), median (IQR)	52 (34, 66) [n=51]	45 (36, 55) [n=45]	46.5 (35, 63) [n=96]
Time from arrival to start of IMP (minutes), median (IQR)	41 (31, 68)	52 (40, 68)	49 (38, 68)
Need for hemostasis control procedure (surgical or radiological), No. %	58 (81.7)	43 (65.1)	101 (73.7)

FiiRST-2 Intervention and active control administration

	Plasma (n = 71)		FC and PCC (n = 66)
Treatment administration			
First pack			
Complete dose, No. (%)	47 (66.2)		59 (89.4)
Partial dose, No. (%)	24 (33.8)		7 (10.6)
Second pack			
Complete dose, No. (%)	21 (29.6)		26 (39.4)
Partial dose, No. (%)	4 (5.63)		7 (10.6)
Not required, No. (%)	46 (64.8)		33 (50)
Dosage of investigational products	**Plasma, units**	**FC, grams**	**PCC, IU**
First pack			
Mean (SD)	3.32 (1.04)	3.94 (0.49)	1856.1 (494.3)
Median (IQR)	4 (2,4)	4 (4,4)	2000 (2000,2000)
Second pack			
Mean (SD)	3.68 (0.8)	3.67 (1.08)	1727.3 (674.2)
Median (IQR)	4 (4,4)	4 (4,4)	2000 (2000,2000)

	Plasma (n = 71)		FC and PCC (n = 66)
Treatment administration			
First pack			
Complete dose, No. (%)	47 (66.2)		59 (89.4)
Partial dose, No. (%)	24 (33.8)		7 (10.6)
Second pack			
Complete dose, No. (%)	21 (29.6)		26 (39.4)
Partial dose, No. (%)	4 (5.63)		7 (10.6)
Not required, No. (%)	46 (64.8)		33 (50)
Dosage of investigational products	**Plasma, units**	**FC, grams**	**PCC, IU**
First pack			
Mean (SD)	3.32 (1.04)	3.94 (0.49)	1856.1 (494.3)
Median (IQR)	4 (2,4)	4 (4,4)	2000 (2000,2000)
Second pack			
Mean (SD)	3.68 (0.8)	3.67 (1.08)	1727.3 (674.2)
Median (IQR)	4 (4,4)	4 (4,4)	2000 (2000,2000)

FiiRST-2 Primary outcome

Table 2 – Units of blood products administered within 24 hours (primary outcome and secondary outcome of blood products administration excluding plasma as control.

	Plasma (n=71)	FC and PCC (n=66)	LS mean ratio (FC + PCC/plasma) 1-sided 97.5% CI)	*P* value
Primary outcome				
Total no. RBC + FP + platelets within 24h, units	23.8 (19.2 - 29.4)	20.8 (16.7 - 25.9)	0.87 (0.0 to 1.19)	0.197
Mean (SD)	23.8 (25.9)	20.8 (26.3)		
Median (IQR)	12.0 (8 to 31)	11.0 (6 to 23)		
Secondary outcome				
Total no. RBC + FP + platelets within 24h, w/o plasma as active control, units	19.1 (15.2 - 24)	20.8 (16.4 - 26.3)	1.09 (0.0 to 1.51)	0.691
Mean (SD)	19.1 (24.2)	20.8 (26.3)		
Median (IQR)	8.0 (5 to 24)	11.0 (6 to 23)		

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Secondary outcome				
Total no. RBC + FP + platelets within 24h, w/o plasma as active control, units	19.1 (15.2 - 24)	20.8 (16.4 - 26.3)	1.09 (0.0 to 1.51)	0.691
Mean (SD)	19.1 (24.2)	20.8 (26.3)		
Median (IQR)	8.0 (5 to 24)	11.0 (6 to 23)		

FiiRST-2 Secondary outcomes (efficacy)

Outcome	Plasma (n=71)	FC and PCC (n=66)	*P* value
Rescue of FC (grams) within 24h, No (%)	42 (59.1)	17 (25.8)	
odds ratio (95% CI)	0.24 (0.12 to 0.5)		0.0001
median (IQR)	4 (0 to 6)	0 (0 to 2)	
Rescue of PCC (grams) within 24h, No (%)	2 (2.82)	3 (4.55)	
odds ratio (95% CI)	1.64 (0.27 to 10.1)		0.59
median (IQR)	0 (0,4000)	0 (0,2000)	
Days out of hospital at day 28, median (IQR)	0 (0 to 7)	0 (0 to 11)	0.19
ICU-free days at day 28, median (IQR)	10 (0 to 19)	11 (0 to 20)	0.40
Ventilator-free days at day 28, median (IQR)	16 (0 to 23)	16 (0 to 24)	0.62

Mortality, No. (%)	**Plasma (n=71)**	**FC and PCC (n=66)**	**Cox Proportional Hazard Model (95%CI)**	***P* value**
24h mortality	12 (16.9)	5 (7.6)		0.24 [a]
All-cause mortality at 28 days	15 (21.1)	9 (13.6)	0.62 (0.26 to 1.40)	0.26 [b]

Outcome	Plasma (n=71)	FC and PCC (n=66)	*P* value
Rescue of FC (grams) within 24h, No (%)	42 (59.1)	17 (25.8)	
odds ratio (95% CI)	0.24 (0.12 to 0.5)		0.0001
median (IQR)	4 (0 to 6)	0 (0 to 2)	
Rescue of PCC (grams) within 24h, No (%)	2 (2.82)	3 (4.55)	
odds ratio (95% CI)	1.64 (0.27 to 10.1)		0.59
median (IQR)	0 (0,4000)	0 (0,2000)	
Days out of hospital at day 28, median (IQR)	0 (0 to 7)	0 (0 to 11)	0.19
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Mortality, No. (%)	**Plasma (n=71)**	**FC and PCC (n=66)**	**Cox Proportional Hazard Model (95%CI)**	***P* value**
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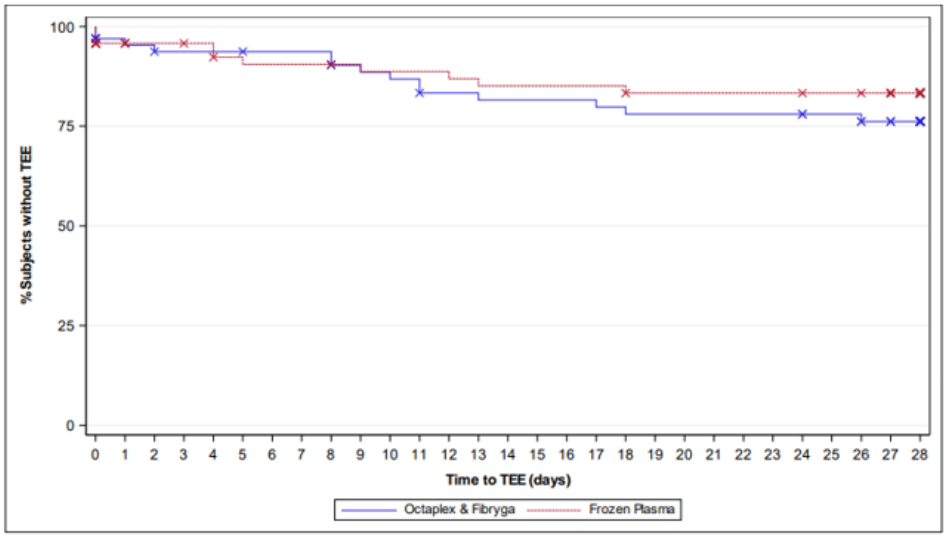
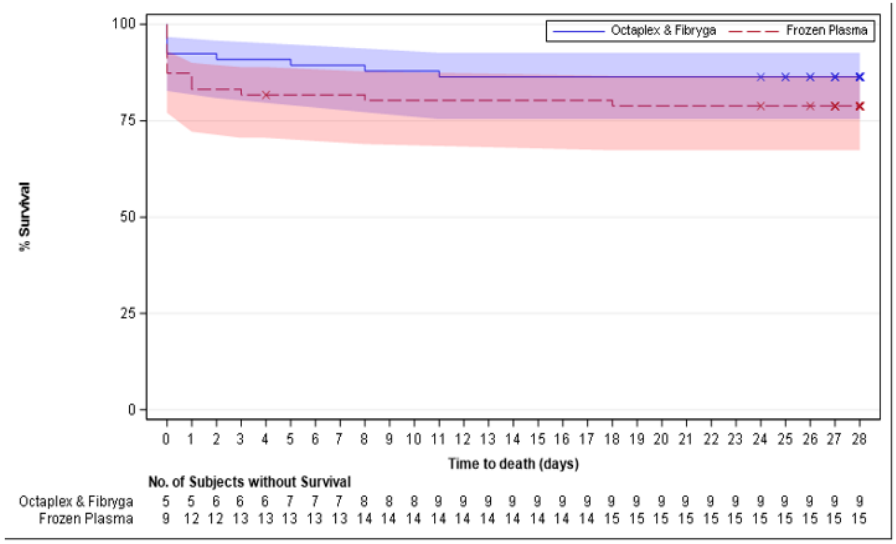
All-cause mortality at 28 days	15 (21.1)	9 (13.6)	0.62 (0.26 to 1.40)	0.26 [b]

FiiRST-2 Secondary outcomes (safety)

Time to thromboembolic event



Time to death



FiiRST-2 Conclusions

- No difference in transfusion outcomes
- No difference in clinical outcomes
- Easier to bedside team to give a complete dose of FC and PCC (lower volume)
- No statistical difference in 24-h and 28-day all cause mortality
- No statistical difference in TE events

FiiRST-2 Limitations

- Variability in threshold for activation + inherent difficult prediction of MT and need for MHP activation:
  - Overactivation of MHP
  - 40% of patients randomized and not treated
- Outliers who consumed greater than 50 to 150 units of blood products (mean [SD] 34.3 [31])
- Differential compliance with IMP administration

FiiRST-2 Strengths

- Design ensured no CFCs were given to patients who did not need
- When plasma and CFCs were administered doses were very close to what was planned
- CFCs and plasma administered 40 minutes earlier compared to PROCOAG and CRYOSTAT-2

Future Directions

- Optimize patient selection (data-driven ML/AI) with continuous vital signs to improve accuracy of early prediction of TIC and need for MHP activation
- Primary outcome – 6, 24-hour mortality
- TE experts as part of the trial design phase; closer FU on TE events; ensure compliance with evidence-based guidelines
- Adjust TE events for time of exposure

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