ORBCoN
Ontario Regional Blood Coordinating Network

Inspiring and facilitating best transfusion practices in Ontario.

# Coagulation factors in trauma resuscitation (PROCOAG/CRYOSTAT/FiiRST2 trial)

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# Faculty Disclosure

***In compliance with CPD policy, Temerty Faculty of Medicine requires the following disclosures to the session audience***

- This program has received no financial external support
- Speaker disclosure:
  - Support for research and honoraria from Octapharma AG
  - Trauma Advisory Board, Haemonetics
  - Support for research from the Department of National Defense, Canada
  - Support for research from the Canadian Institutes for Health Research (CIHR)

# Objectives

- Brief on clotting factors concentrate use in trauma resuscitation - PROCOAG, CRYOSTAT and FiiRST-2 Trials
- Some data on FiiRST-2

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Efficacy and Safety of Early Administration of 4-Factor Prothrombin Complex Concentrate in Patients With Trauma at Risk of Massive Transfusion

## The PROCOAG Randomized Clinical Trial

Pierre Bouzat, MD, PhD; Jonathan Charbit, MD; Paer-Selim Abback, MD; Delphine Huet-Garrigue, MD; Nathalie Delhaye, MD; Marc Leone, MD, PhD; Guillaume Marcotte, MD; Jean-Stéphane David, MD, PhD; Albrice Levrat, MD; Karim Asehnoune, MD, PhD; Julien Pottecher, MD, PhD; Jacques Duranteau, MD, PhD; Elie Courvalin, MD; Anais Adolle, MSc; Dimitri Sourd, MSc; Jean-Luc Bosson, MD, PhD; Bruno Riou, MD, PhD; Tobias Gauss, MD; Jean-François Payen, MD, PhD; for the PROCOAG Study Group

- **Question:** Does 4F-PCC reduce 24h ABP transfusion in adult trauma patients at risk of massive transfusion compared to placebo?
- Double-blind RCT, placebo-controlled, superiority trial
- In 12 French L1 trauma centers
- Consecutive patients with trauma at risk of massive transfusion
  - **At risk** = 1U prehospital blood products or within 1h of admission AND an ABC Score ≥ 2 OR clinician thinks patient will need MT
  - **Massive transfusion** = 3U blood products within 1h of admission or at least 10U within the first 24 hours
  - **ATC** = PT >1.2 and **Severe ATC** = PT >1.5

# PROCOAG – design

- **Inclusion:**
  - ≥18 years of age)
  - **Directly from scene**
  - At risk for massive transfusion
- **Exclusion:**
  - **Traumatic cardiac arrest**
  - **Traumatic cardiac arrest before randomization**
  - **Patients expected to die within the first hour of admission**
  - Transfers
  - On anticoagulants
  - Known pregnancy
  - Known hypersensitivity to 4F-PCC
  - Known pre-injury terminal condition
  - Patients under guardianship
  - Any inclusion in another trial within the last 30 days
  - Patients without health insurance

# PROCOAG – design

- **All patients received trauma resuscitation management including:**
  - Restricted crystalloid fluid expansion
  - RBCs:FFP in a ratio of 1:1 to 2:1
  - TXA within 3h after injury (1g bolus + 1g over 8 h)
  - Early hemorrhage control
  - FC fibrinogen level <1.5g/L OR VET with functional deficiency
  - Platelets to keep >50 x $10^9$/L
- **Patients randomized within 1 hour of arrival to:**
  - 4F-PCC: 1mL/kg (25IU)
  - Placebo: 1mL/kg of NS 0.9%
  - Given at 120mL/h

# PROCOAG – outcomes

- **Primary outcome:**
  - Efficacy: Median 24hr all product consumption (RBC, FFP, and Platelets)
- **Secondary:**
  - **Safety: Arterial or venous thromboembolic events (PE, DVT, Stroke, MI, Mesenteric Ischemia, and Extremity Ischemia) through day 28**
  - Individual blood component units consumed within first 24 hours
  - Time to PT <1.5 (severe ATC)
  - Time to hemorrhage, Time to hemorrhage control
  - 24hr and 28d mortality
  - ICU free days, Ventilator free days, Hospital free days through 28 days

# PROCOAG - results

- **4313 trauma patients evaluated:**
  - 350 were eligible for emergency inclusion
  - 327 patients were randomized
  - 324 patients were analyzed
- **Patient Characteristics:**
  - Median age: 39 years (Range 27 to 56)
  - **ISS: 36 (Range 26 to 50)**
  - Blunt Trauma ≈80% of patients
  - **Transfusion of ≥10U Blood Products ≈27%**
  - **Lactate Level: 4.6mmol/L (Range 2.8 to 7.4)**
  - **Prehospital SBP <90mmHg: 59% of patients**

# PROCOAG - results

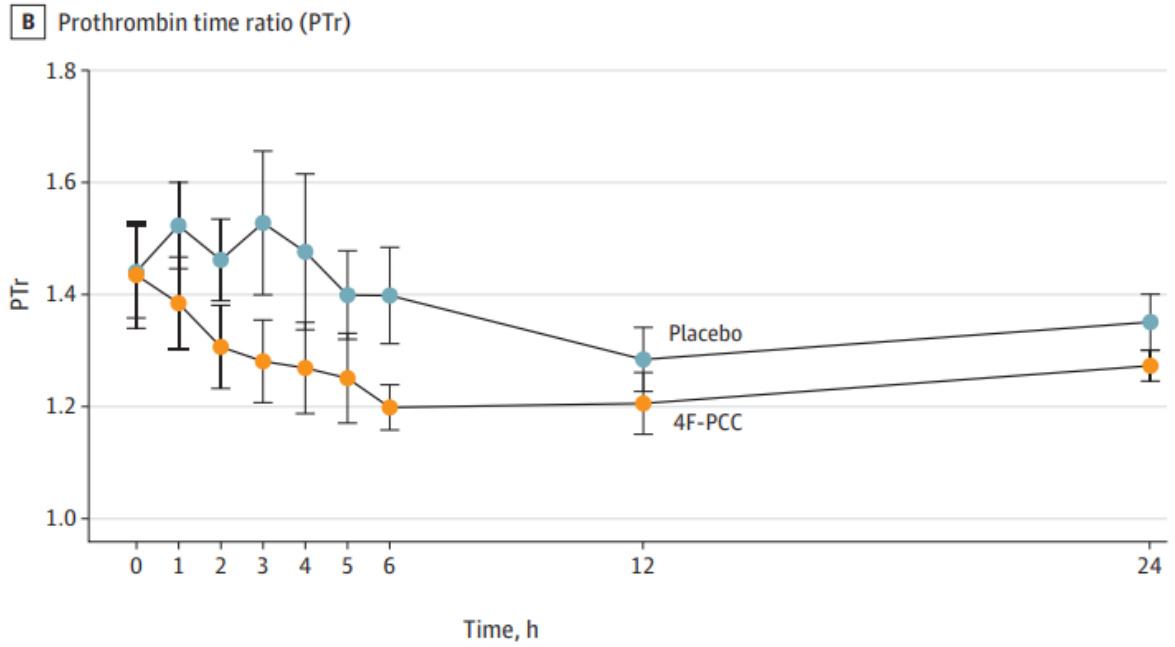
- **Primary Outcome:**
  - **4F-PCC: 12U (Range 5 to 19)**
  - **Placebo: 11U (Range 6 to 19)**
  - Absolute Diff: 0.2U; 95% CI-2.99 to 3.33; P = 0.72
  - ***NOT STATISTICALLY SIGNIFICANT***
  - Also, no difference in individual components given
- **Thromboembolic Events:**
  - **4F-PCC: 35%**
  - **Placebo: 24%**
  - **Absolute Diff: 11%; 95% CI 1 to 21%**
  - **Relative Risk 1.48; 95% CI 1.04 to 2.10; P = 0.03**
  - ***STATISTICALLY SIGNIFICANT***
- No differences between groups in any other secondary outcomes

# Take away points

- **Blinding –** only unblinded was the nurse preparing PCC
- **Blinding –** PCC and placebo administered in opaque syringes to avoid unblinding
- **Survivor bias –** Unlikely to have for the primary outcome. After complete patient enrollment and before data analysis the authors confirmed that the time spent in the study (up to 24 hours) did not differ between the 2 groups

# Take away points

- **PT ratio –** goes down faster in PCC group



# Take away points

- **Mortality –** Very low rate, 11%:
  - In a very sick population
  - ↑ proportion of patients received TXA in the prehospital setting
- **TXA –** Placebo group received in 86% vs. 76% in PCC group
- **FC –** ↑ median dose in placebo vs. PCC group. Dilution of PCC effect?

# Take away points

- PCC + FFP given without VET – exposed patients w/o TIC to the risk of coagulation factor "overdosing"
- Prehospital care is different from North America (SAMU) – "stay and play"
- Higher % of patients in shock (59% with prehospital SBP <90mmHg vs 30 to 45% in 2 previous non-randomized studies and the RETIC trial

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury

## The CRYOSTAT-2 Randomized Clinical Trial

Ross Davenport, PhD; Nicola Curry, MD; Erin E. Fox, PhD; Helen Thomas, MSc; Joanne Lucas, MSc; Amy Evans, MMedSci; Shaminie Shanmugaranjan, BSc; Rupa Sharma, BSc; Alison Deary, MSc; Antoinette Edwards, MA; Laura Green, MD; Charles E. Wade, MD; Jonathan R. Benger, MD; Bryan A. Cotton, MD; Simon J. Stanworth, MD, DPhil; Karim Brohi, MD; for the CRYOSTAT-2 Principal Investigators

- **Question:** Does transfusion of early and empiric high-dose cryoprecipitate in addition to standard care improve survival in bleeding patients with trauma who require MHP?
- Randomized, open-label, parallel-group, controlled, international, phase 3, multicenter study
- 26 UK and US major trauma centers
- Adult trauma patients requiring MHP:
  - Evidence of active hemorrhage – SBP < 90mmHg at any time AND
  - At least 1U of any blood component

# CRYOSTAT-2 – design

- Patients within 90 minutes of randomization and 3 hours of injury were randomized to:
  - **Standard care:** 1:1:1 RBC:FFP:Platelets
  - **Cryoprecipitate**: Standard care + 3 pools of cryoprecipitate (6g fibrinogen equivalent)

# CRYOSTAT-2 – inclusion/exclusion

- **Inclusion:**
  - Adult trauma patient (≥16 years of age)
  - Severe injury with evidence of active hemorrhage requiring activation of local MHP
  - Started or received at least 1U of any blood component
  - SBP<90mmHg at any point
- **Exclusion:**
  - Patient being transferred from another hospital
  - Injuries incompatible with life as assessed by the TTL
  - >3hrs elapsing from the time of injury

# CRYOSTAT-2 – outcomes

- **Primary outcome:**
  - All-cause mortality at 28d (intention to treat population)
- **Secondary outcomes:**
  - 25 Prespecified outcomes
  - Safety: Thrombotic events at 28d
  - Efficacy outcomes
  - Quality of life

# CRYOSTAT-2 – results

- **1604 eligible patients:**
  - 1531 (95%) of patients were included in the primary analysis population
  - Most patients recruited from UK (1555 patients); US recruited 49 patients
  - Median Age: 39 years (26 to 55years)
  - Median ISS: 29 (18 to 43)
  - Penetrating Injury: 36%
  - Blunt Injury: 64%
  - SBP <90mmHg at Hospital Arrival: 33%

# CRYOSTAT-2 – results

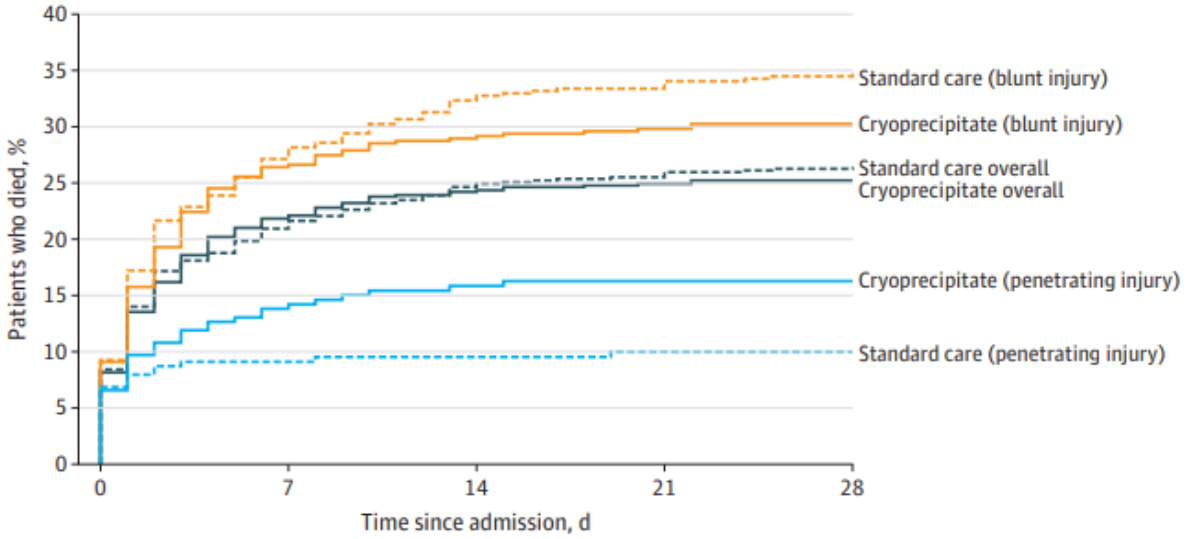
- **Timing/Interventions:**
  - Prior to hospital arrival:
    - 43% received a blood component
    - 79% received TXA (96% of patients received TXA either before or in the hospital)
  - Median time from injury to ED arrival: 76 mins
  - Median time from admission to randomization: 15 mins
  - **85% of patients in cryoprecipitate group received cryoprecipitate vs 32% in the standard care group**
  - **Median time from admission to first adm. cryo: 68mins (cryoprecipitate group) vs 120min (standard care group)**

# CRYOSTAT-2 – results

- **All-Cause 28-d Mortality:**
  - Standard Care Group: 26.1%
  - Cryoprecipitate Group: 25.3%
  - **OR 0.96; 95% CI 0.75 to 1.23; p = 0.74**
- **Mortality at 6 h and 24 h was similar between groups**
- **The proportion of deaths from bleeding in the 1st 6th and 24 h was not different between groups**
- Median time to death from hemorrhage:
  - 191 mins in cryoprecipitate group vs
  - 86 mins in the standard care group

# CRYOSTAT-2 – results

**Figure 2. Mortality Overall and by Injury Type**




| No. of patients at risk | | | | | |
|---|---|---|---|---|---|
| Cryoprecipitate overall | 784 | 567 | 532 | 514 | 498 |
| Standard care overall | 795 | 569 | 518 | 501 | 479 |
| Cryoprecipitate (blunt injury) | 495 | 348 | 332 | 323 | 310 |
| Standard care (blunt injury) | 518 | 353 | 320 | 307 | 289 |
| Cryoprecipitate (penetrating injury) | 289 | 219 | 200 | 191 | 188 |
| Standard care (penetrating injury) | 277 | 216 | 198 | 194 | 190 |

The median number of days observed was 28 days for all groups. Mortality at day 28 was analyzed as a binary outcome with odds ratios, 95% CIs, and *P* values reported in the results and in Figure 3.

# CRYOSTAT-2 – results

- Penetrating trauma 28-day mortality: significantly higher in the cryoprecipitate group than the standard care group (16.2% vs 10%; OR 1.74; 95% CI 1.20 to 2.51)
- No difference in safety outcomes, incidence of thrombotic events, or transfusion requirements between groups

# Take away points

- **Very sick cohort –** Severely injured, hypotensive, and received substantial blood component transfusions
- **Convenience sample –** Could cause selection bias (888 patients not randomized due to unavailability of research team)
- **Lack of a placebo group –** Difficult to examine the effect of timing of cryoprecipitate administration on outcomes (adding more fibrinogen to a protocol that already uses possibly provides less benefit)

# Take away points

- **Protocol violations –** 434/799 patients received the intervention (bias towards the null)
- **Convenience sample –** Could cause selection bias (888 patients not randomized due to unavailability of research team + 206 w/o reason reported)
- **Lack of a placebo group –** Difficult to examine the effect of timing of cryoprecipitate administration on outcomes (adding more fibrinogen to a protocol that already uses possibly provides less benefit)

# Take away points

- **Cross-over between groups –** 15% of patients in the cryo group did not receive cryo and 9% of patients in the standard care group got cryo within 90 minutes (32% within 24 hours). This could dilute any beneficial effects seen
- **Fibrinogen level before cryo –** Some patients may have received cryoprecipitate without having low fibrinogen levels
- **28-day mortality in penetrating trauma –** 16.2% vs 10%; OR 1.74; 95% CI 1.20 to 2.51).
  - Secondary outcome, hypothesis generating
  - Requires further research

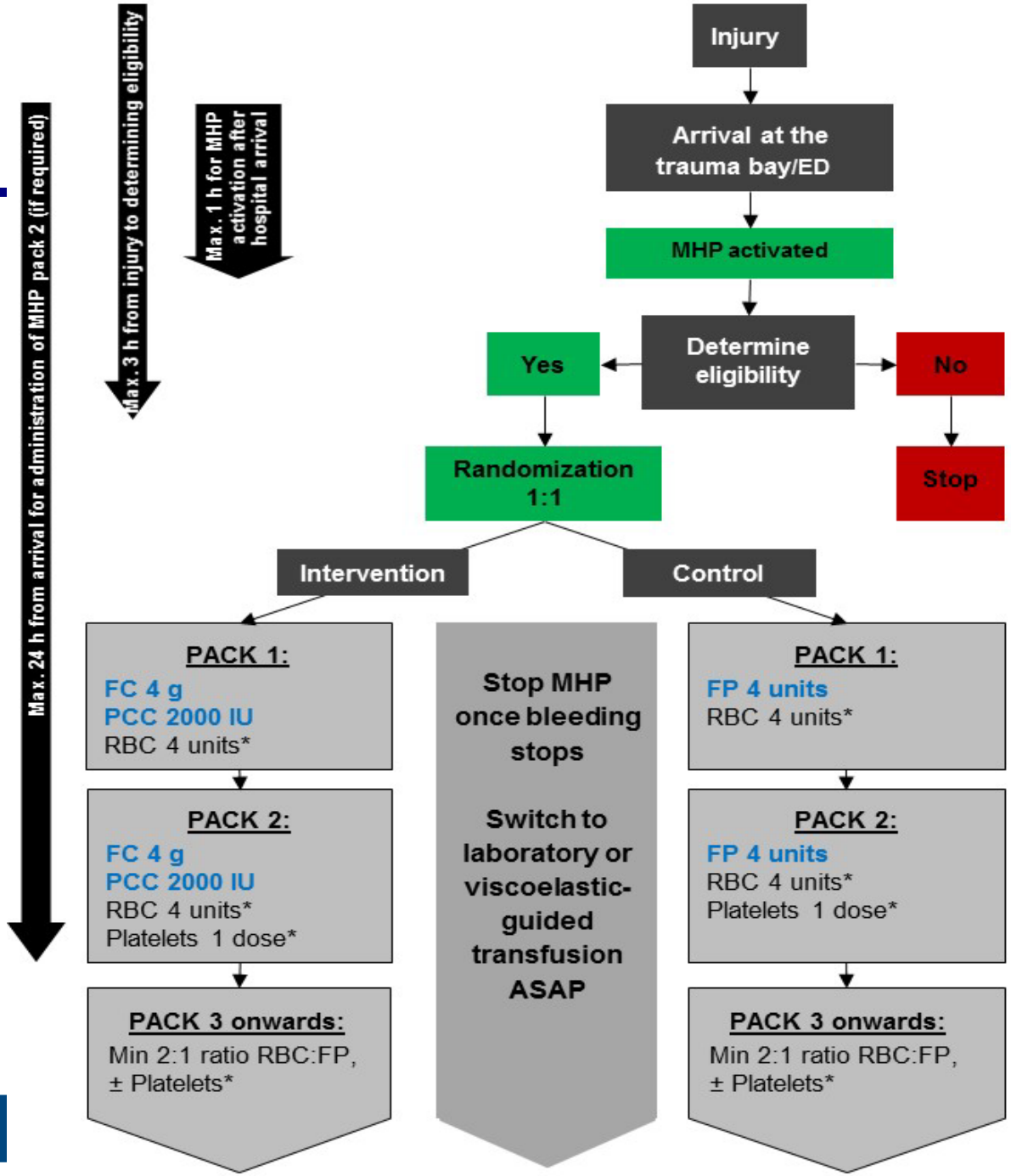
BMJ Open

# Protocol for a multicentre, randomised, parallel-control, superiority trial comparing administration of clotting factor concentrates with a standard massive haemorrhage protocol in severely bleeding trauma patients: the FiiRST 2 trial (a 2020 EAST multicentre trial)

Luis Teodoro da Luz ,[1,2] Jeannie Callum,[3] Andrew Beckett,[2,4] Hans-Peter Hucke,[5] Jo Carroll,[6] Deep Grewal,[6] Bruce Schwartz,[7] Henry Peng,[8] Paul T Engels,[9] Neil Parry,[10] Andrew Petrosoniak,[11] Homer Tien,[1] Avery B Nathens,[1] Damon Scales,[12] Keyvan Karkouti[13]

# FiiRST-2 Trial

- Multicenter RCT
- 11 Level 1 Trauma Centers across Canada (6 enrolled patients)
- 350 MHP patients
- Superiority trial
- **Adaptive design:**
  - Interim analysis
  - Recalculation of sample size and power
- **Primary outcome:**
  - Number of units of ABPs < 24 h
- **Secondary outcomes:**
  - Hemostasis
  - Efficacy
  - Safety


Max. 24 h from arrival for administration of MHP pack 2 (if required)
Max. 3 h from injury to determining eligibility
Max. 1 h for MHP activation after hospital arrival
Injury
Arrival at the trauma bay/ED
MHP activated
Determine eligibility
Yes
No
Stop
Randomization 1:1
Intervention
Control
PACK 1:
FC 4 g
PCC 2000 IU
RBC 4 units*
PACK 2:
FC 4 g
PCC 2000 IU
RBC 4 units*
Platelets 1 dose*
PACK 3 onwards:
Min 2:1 ratio RBC:FP, ± Platelets*
Stop MHP once bleeding stops
Switch to laboratory or viscoelastic-guided transfusion ASAP
PACK 1:
FP 4 units
RBC 4 units*
PACK 2:
FP 4 units
RBC 4 units*
Platelets 1 dose*
PACK 3 onwards:
Min 2:1 ratio RBC:FP, ± Platelets*

| Complete the following: | | ☑ | |
|---|---|---|---|
| | **Inclusion Criteria** | **Yes** | **No** |
| 1 | Estimated age greater than 16 years old. | ☐ | ☐ |
| 2 | Severely injured (penetrating or blunt) trauma patients. | ☐ | ☐ |
| 3 | Triggered MHP within first hour of hospital arrival at the trauma bay/ED. | ☐ | ☐ |
| | **Exclusion Criteria** | **Yes** | **No** |
| 4 | Have received more than 2 U RBCs during the pre-hospital phase of care. | ☐ | ☐ |
| 5 | Have received more than 2 U RBCs in the trauma bay/ED before activation of the MHP. | ☐ | ☐ |
| 6 | Have an elapsed time from injury of more than 3 hours. | ☐ | ☐ |
| 7 | Have a penetrating traumatic brain injury with Glasgow Coma Scale (GCS) of 3. | ☐ | ☐ |
| 8 | Are suspected or known to be on anticoagulants in the last 7 days. | ☐ | ☐ |
| 9 | Have known congenital or acquired bleeding disorders. | ☐ | ☐ |
| 10 | Have a known pregnancy. | ☐ | ☐ |
| 11 | Refuse blood transfusion due to religion or other reasons. | ☐ | ☐ |
| 12 | Previous history of heparin induced thrombocytopenia (HIT). | ☐ | ☐ |

# FiiRST-2 – Developments

- Launched in April 2021
  - Consistent enrollment
  - Trial procedures going ok

# FiiRST-2 – Developments

- L[illegible]hed in April 2021

MHP OVERACTIVATION

- Direct feedback to TTL
- MHP audit process:
  - 25% of over activation
  - Education at TTL subcommittee meetings
  - Education during trauma bay orientation to trainees
  - Education at video review rounds

# FiiRST-2 – Developments

- L[illegible]hed in April 2021

# FiiRST-2 – Developments

- L[illegible]hed in April 2021

WHEN CALLING BLOOD BANK, SAY:
"Patient is eligible for the study" OR
"Patient is not eligible for the study due to..."

MHP OVER[illegible]

[illegible] (busy)

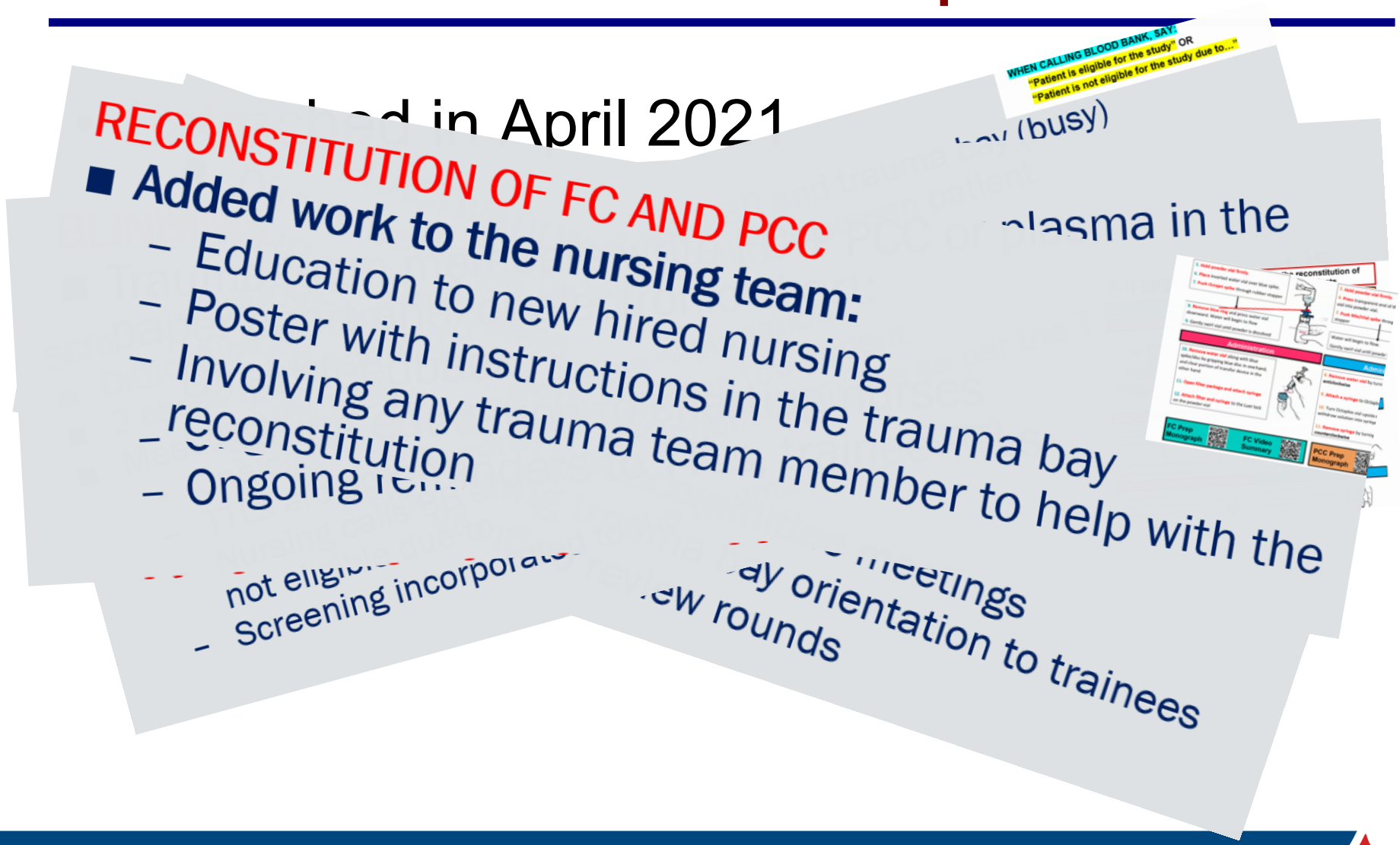
BLINDING

- Trauma team members write FC + PCC or plasma in the paper chart and/or electronic chart:
  - Direct feedback
  - Ongoing education to charting nurses
  - Ongoing reminders to TTLs, trainee TTLs


not eligi[illegible]
Screening incorporat[illegible]

[illegible] meetings
[illegible]ay orientation to trainees
[illegible]ew rounds

# FiiRST-2 – Developments



# T-2 – Developments

2021

CONSENTING:

- Check with MRP prior to approaching SDM/patient

RE

- Added
  - Educa
  - Poster with
  - Involving any tra
  - reconstitution
  - Ongoing

not eligi
Screening incorporat

(busy)

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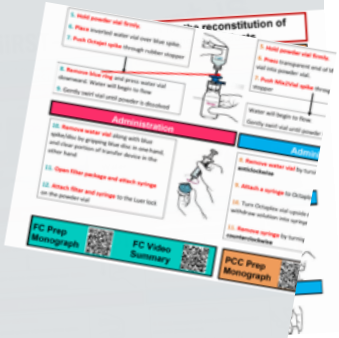
ew round

WHEN CALLING BLOOD BANK, SAY:
"Patient is eligible for the study" OR
"Patient is not eligible for the study due to..."



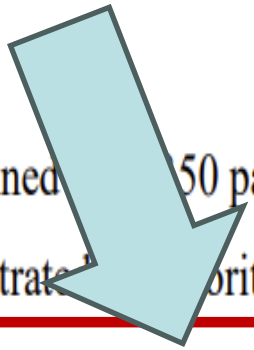
# FiiRST-2 – Developments

- IDSMC assessments at each 60 patients
- First IDSMC – passed
- 6 sites enrolling by Feb 2023
- IDSMC meeting Feb 2023

# FiiRST-2 – Developments

| As of January 31st, 2023 | Sunnybrook | St. Mike's | Hamilton | London | Vancouver | Kingston | Totals | Change since last meeting |
|---|---|---|---|---|---|---|---|---|
| Status | Enrolling | Enrolling | Enrolling | Enrolling | Enrolling | Enrolling | | |
| **Total Code Transfusions** | **279** | **110** | **42** | **113** | **1** | **18** | **563** | +175 |
| **Not Screened** | **18** | **56** | **24** | **23** | **0** | **3** | **124** | +31 |
| **Total Screened** | **261** | **54** | **18** | **90** | **1** | **15** | **439** | +144 |
| Not Randomized | **112** | **28** | **11** | **60** | **0** | **10** | **221** | +82 |
| Randomized | **149** | **26** | **7** | **30** | **1** | **5** | 218 | +62 |
| **(1) Consented** | **80** | **15** | **4** | **16** | **1** | **3** | 119 | +40 |
| **(2) Pending Consent** | **0** | **0** | **0** | **1** | **0** | **0** | 1 | -11 |
| **(3) Refused** | **11** | **0** | **0** | **0** | **0** | **0** | 11 | +3 |
| **(4) Pt Expired/ Unable to reach SDM** | 14 | 7 | 0 | 1 | 0 | 0 | 22 | +9 |
| **(5) No IMP administered** | **44** | **4** | **3** | **12** | **0** | **2** | 65 | +21 |

# Stopping rules



- To continue the trial as planned 50 patients have completed the study,
- To stop the trial for demonstrat ority at the interim analysis,
- To stop the trial at the interim for futility (e.g. conditional power less than 25%) or for requiring an increase in sample size that is considered unfeasible (e.g. total sample size larger than 450),
- To continue the trial with a modified sample size.

# FiiRST-2 Trial

**Some blinded data**

# FiiRST-2 Trial

## Summary of enrollment

| Site # | Name | Randomized | Received Treatmen | Consented | pending | Pt expired & Unable to contact SDM Collect all Data | No product | Was IMP released | Refused |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Sunnybrook | 148 | 105 | 80 | 0 | 14 | 43 | 0 | 11 |
| 2 | St. Mike's | 26 | 17 | 10 | 0 | 7 | 9 | 3 | 0 |
| 3 | Hamilton | 7 | 4 | 4 | 0 | 0 | 3 | 0 | 0 |
| 4 | London/Victoria Hospital | 30 | 18 | 17 | 0 | 1 | 12 | 0 | 0 |
| 5 | Vancouver-VGH | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| 6 | Kingston-Victoria | 5 | 3 | 3 | 0 | 0 | 2 | 0 | 0 |
| | Total: | 217 | 148 | 115 | 0 | 22 | 69 | 3 | 11 |
| | | | | | Total # of Evaluable Patients: | 137 | | | |
| | | | | | 0.68 | % of randomized patients who were treated | | | |
| | | | | | 0.93 | % of treated patients who are fully Evaluable | | | |
| | | | | | 0.63 | % of randomized patients who are fully Evaluable | | | |

# FiiRST-2 Trial

## Randomization – FC+PCC vs Plasma

| | Planned treatment group | | | |
|---|---|---|---|---|
| | Octaplex & Fibryga | Frozen Plasma | Not Assigned | Total |
| Analysis population | N | N | N | N |
| Enrolled | 106 | 110 | 1 | 217 |
| Randomized | 106 | 110 | 0 | 216 |
| Consented (incl. REB Approval) | 69 | 74 | 0 | 143 |
| Intention To Treat (ITT) Population | 66 | 71 | 0 | 137 |
| Modified Intention To Treat (ITT) Population | 66 | 71 | 0 | 137 |

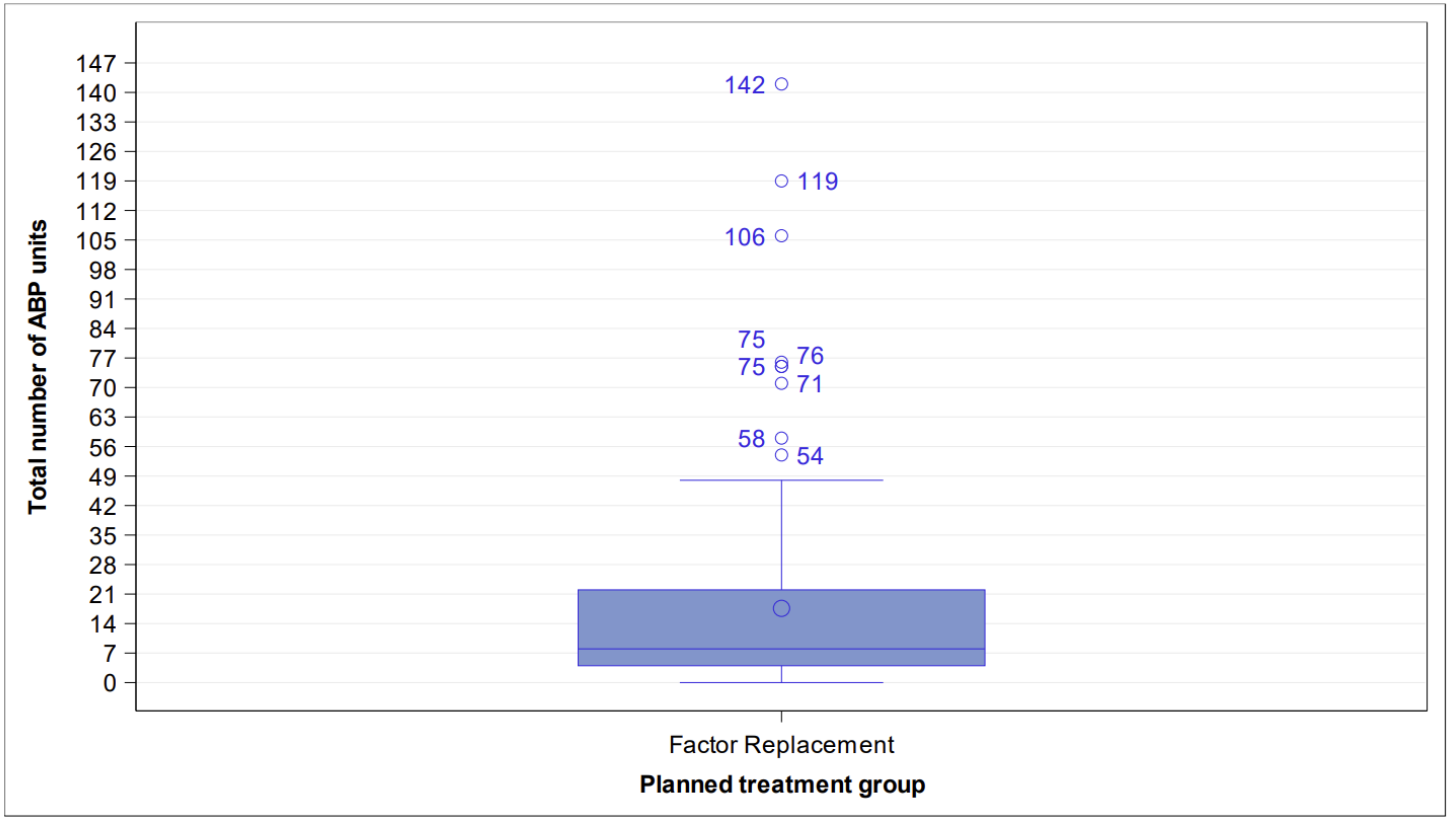
# FiiRST-2 Trial

## Distribution of total ABPs within 24 h

| Total number of ABP units | Planned treatment group | | Total | |
|---|---|---|---|---|
| | Factor Replacement | | | |
| | N | % | N | % |
| 0 units | 2 | 1.68 | 2 | 1.68 |
| 1-5 units | 43 | 36.13 | 43 | 36.13 |
| 6-10 units | 25 | 21.01 | 25 | 21.01 |
| 11-20 units | 18 | 15.13 | 18 | 15.13 |
| 21-50 units | 22 | 18.49 | 22 | 18.49 |
| >50 units | 9 | 7.56 | 9 | 7.56 |
| Total | 119 | 100.00 | 119 | 100.00 |

# FiiRST-2 Trial

## Box plot – total ABPs within 24 h



# FiiRST-2 Trial

## Number of total ABPs within 24 h

| Planned treatment group | Total allogeneic blood products (units) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | Std | Min | Q1 | Median | Q3 | Max |
| Factor Replacement | 119 | 17.6 | 24.0 | 0 | 4.0 | 8.0 | 22.0 | 142 |
| Total | 119 | 17.6 | 24.0 | 0 | 4.0 | 8.0 | 22.0 | 142 |

# FiiRST-2 Trial

| Blood product / Planned treatment group | | Total allogeneic blood products (units) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | Std | Min | Q1 | Median | Q3 | Max |
| FP | Factor Replacement | 119 | 3.3 | 7.1 | 0 | 0.0 | 0.0 | 4.0 | 43 |
| | Total | 119 | 3.3 | 7.1 | 0 | 0.0 | 0.0 | 4.0 | 43 |
| PLT | Factor Replacement | 119 | 4.5 | 7.0 | 0 | 0.0 | 0.0 | 8.0 | 40 |
| | Total | 119 | 4.5 | 7.0 | 0 | 0.0 | 0.0 | 8.0 | 40 |
| RBC | Factor Replacement | 119 | 9.8 | 11.0 | 0 | 4.0 | 6.0 | 11.0 | 67 |
| | Total | 119 | 9.8 | 11.0 | 0 | 4.0 | 6.0 | 11.0 | 67 |

# FiiRST-2 Trial

## Box plot – total ABPs within 24 h

Table 3-1
Number of subjects without survival at 6h / 24h / 28 days after arrival at the trauma bay / ED
(All allowed and treated subjects, N=128)

| Planned treatment group | Death during time interval after arrival at the trauma bay / ED | | | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Alive | | Before | | Within 6 h | | After 6 h up to 24 h | | After 24 h up to 28 days | | | |
| | N | % | N | % | N | % | N | % | N | % | N | % |
| Factor Replacement | 106 | 82.81 | 0 | 0.00 | 13 | 10.16 | 3 | 2.34 | 6 | 4.69 | 128 | 100.00 |
| Total | 106 | 82.81 | 0 | 0.00 | 13 | 10.16 | 3 | 2.34 | 6 | 4.69 | 128 | 100.00 |

17% mortality
Mostly first few hours
None of the descriptions appear IMP related

# THANK YOU

# Challenges in trauma trials

INDEPENDENT SUBMISSION

A systematic review and meta-analysis of sample size methodology for traumatic hemorrhage trials

**Jamie Ghossein, MD, Shannon M. Fernando, MD, MSc, Bram Rochwerg, MD, MSc, Kenji Inaba, MD, Jacinthe Lampron, MD, MPH,** *and* **Alexandre Tran, MD, MSc**, *Ottawa, Canada*

- Well done SR and meta-analysis
- Highlights common limitations in sample size calculations which limits the potential impact of these trials in clinical practice and results in wasted research resources

# Challenges in trauma trials

- 13 RCTs included, superiority trials
- Only 2 demonstrated positive results (CRASH-2/PAMPer)
- Remaining:
  - 8 (73%) were terminated early
  - Most common reason was futility
- Concerning findings when calculating N:
  - Overestimation of expected treatment effects
  - Often based on small pilot / feasibility studies
    - Imprecise estimation of treatment effect
    - Disregard minimal effect size meaningful to patients

# Challenges in trauma trials

- CRASH-2 was the only study that included a justification for a minimally important difference
- **Prognostic enrichment:**
  - Strategy to select patients with a higher likelihood of a disease related outcome
  - They can inform more precise estimates and decrease heterogeneity at baseline risk
- **Minimally important difference:**
  - Strategy where the target treatment effect size is based on a minimum value that would provide a meaningful clinical difference to the patient
    - Plausible treatment effect
    - Important to patient and not only based on assumptions or pilot studies

# Challenges in trauma trials

- **Problem:**
  - Pragmatic risk stratification of bleeding trauma patients is known to be very challenging:
    - Poor performance of clinical gestalt
    - Lack of well validated prediction models

→ Target a less heterogeneous study population

→ Improve statistical efficiency

→ Reducing required sample size

# Challenges in trauma trials

- **Many other challenges:**
  - Funding that allow adequately powered trials
  - Difficulty to assess the effect of an intervention in a heterogeneous patient population
  - Difficulty in assessing the generalizability of interventions given significant differences between trauma centers
  - Consent
  - Difficulty in choosing adequate outcome measures
  - Lack of long term follow up
  - Threats to internal validity