STORHM Study

French Whole Blood Trial in Traumatic Massive Hemorrhage

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Disclaimer:
The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the French Department of Defense.

Conflict of interest:
None

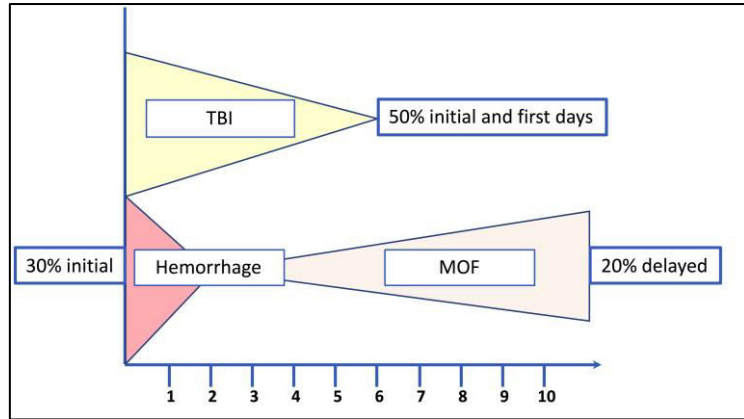# The FMBI is responsible for blood supply to armed forces
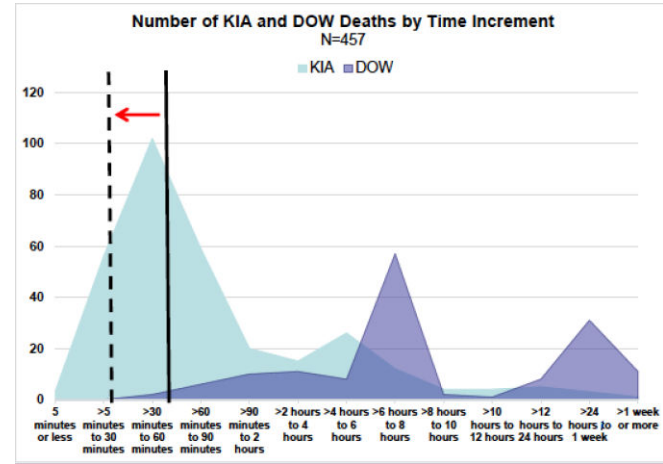

- Logistical issues
- War injuries

Massive hemorrhage kills and requires blood

Keene et al. J R Army Med Corps 2016

Andre Cap, NATO Blood Panel Meeting 2017

Transfusion Ratio	Low FFP, Low PLT	High FFP, Low PLT	Low FFP, High PLT	High FFP, High PLT
Odds ratio (95% confidence interval)	1.000	0.759	0.343	0.220
n	1,369	1,197	82	980
Nonsurvivors, %	17	17	16	12*
ISS	16	21†	22†	26†
IQR	10–22	14–29	14–29	18–34

Pidcoke et al. J Trauma 2012

Blood is for bleeding
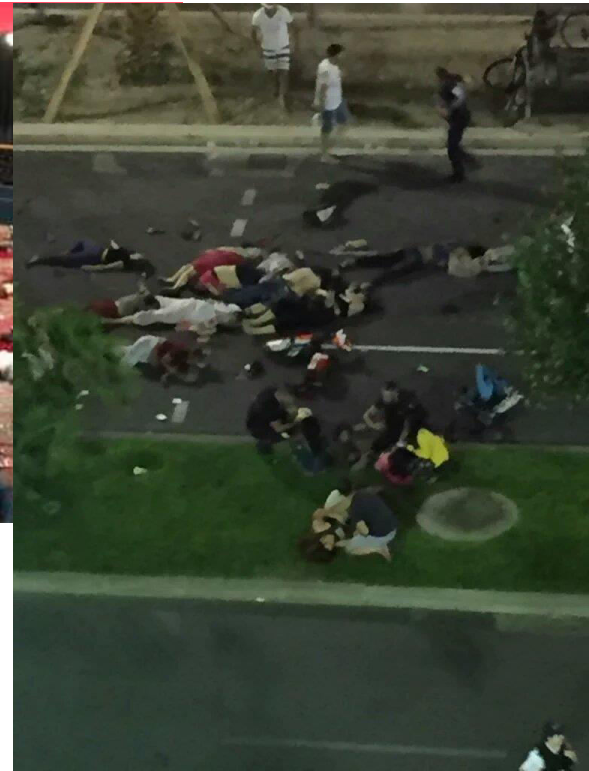Saltwater is for cooking pasta

P. Spinella 2017

What leads us to interfere with civilians settings

Saint-Michel – 1995

Bataclan – 2015

Nice – 2016

Victims of terrorist attacks

- Suffered from war injuries
- Required blood

We implemented component therapy and ratios

- **Massive transfusion protocol**
  - Pack 1
    - 3 pRBCs
    - 3 plasma
  - Pack 2 and beyond
    - 1 platelets unit
    - 3 pRBCs
    - 3 plasma

You will need a lot of blood... products

TABLE 2. Guidance for blood component use during the 2012 London Olympics

Priority	RBCs (U)	FFP (U)	PLTs*	Cryoprecipitate (pool of 5 donations)	Category definition
P1	10	6	1	1-2	Immediate, requiring immediate intervention
P2	4	0	0	0	Urgent, requiring intervention < 6 hr
P3	0	0	0	0	Delayed, walking wounded

* PLT minimum dose of 2.4×10^{11} per adult therapeutic dose (Ref: internal reporting to NHSBT by H. Doughty).

Type of injury	Number of casualties	Total RBCs received	Mean initial RCC	Median Initial RCC
Single leg amputation	3	34	11·3	13
Bilateral leg amputation	5	117	23·4	18
Crush Injury	1	10	10	10
Trauma/Blast Injuries	7	83	11·8	3
Unknown	9	92	10·2	4
Total	25	336		

Doughty et al. Transfusion 2016 – Glasgow et al. Transf Med 2012

What were the consequences in Paris

- MMC Percy and Bégin
- November 2015 attacks
- **52 patients - 3 hours**
  - 33 need blood (8P1 + 22P2+ 3TM)
  - **147 blood products**

- **Time to transfusion in these patients**
  - Among the more severely injured patients (with an ISS > 15)
  - **FFP: 180** min [73-260]
  - **pRBC: 90** min [40-125]
- **Time to transfusion** in "usual situations"
  - **FFP: 78 min**

<div style="border: 2px solid red; color: red; text-align: center;">

Only 37% of patients requiring MT
received plasma within the first hour after admission
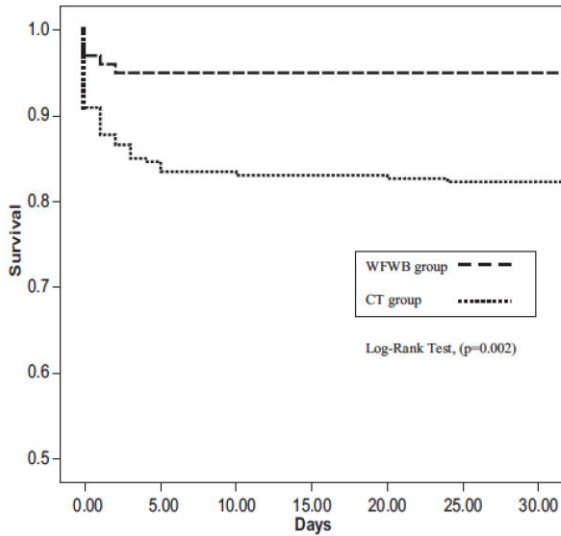
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What are the solutions?

Time to transfusion (min-IQR)	FLyP	FFP	n
N'Guyen 2018	**15** [10-25]	**95** [70-145]	72
Garrigue 2018	**37** [24-82]	**91** [85-106]	45

N'Guyen et al. J Trauma 2018 – Garrigue et al. J Thromb Haemost 2018

Advantages of whole blood use in these patients

	MWB Composite		1:1:1		
	n = 18	SD	n = 23	SD	p
INR	1.32	0.14	1.31	0.18	0.8232
PT, s	56.35	16.71	41.76	4.68	0.0117
PTT, s	16.09	1.35	15.98	1.71	0.7858
Factor II, %	71.94	9.61	65.00	19.81	0.0848
Factor V, %	50.33	16.89	50.91	21.56	0.4942
Factor VII, %	72.00	14.73	62.26	27.41	0.1032
Factor VIII, %	57.22	24.99	76.35	32.17	0.0201
Factor IX, %	84.28	15.37	86.22	25.39	0.6453
Factor X, %	73.00	13.17	66.52	16.12	0.1648
ATIII, %	77.22	18.49	72.65	41.19	0.0697
Protein C, %	83.56	13.30	75.52	24.53	0.1891
Fibrinogen, mg/dL	221.06	41.22	241.65	67.16	0.2345
D-dimer, µg/mL	4.01	5.87	0.25	0.06	0.0026
EXTEM CT, s	202.94	138.22	145.91	42.81	0.2319
EXTEM CFT, s	207.17	125.82	760.57	1560.60	0.7426
EXTEM α, degrees	56.78	14.07	56.27	16.00	0.8489
EXTEM a10, mm	45.00	11.10	38.57	14.04	0.1094
EXTEM a20, mm	55.11	9.37	45.83	15.45	0.0088
EXTEM MCF, mm	61.17	5.07	50.35	15.48	0.0005

	Whole Blood	Component Therapy 1:1:1
Hemoglobin g/dL	12 – 13	9
Platelets (G/L)	138 – 165	90 – 120
Coagulation proteins	Normal	60% dilution
TEG	Normal	Reduced
PLT aggregation	≥ 50% baseline D7-10 at 4°C	Nearly complete loss D5 in 22°C-PLT
Anticoagulant and additive solutions(mL/6U)	378	1055
Practical aspects	**6 bags** One storage mode	**13 bags** 3 storage modes

Spinella et al. J Trauma 2009   *Kornblith et al. J Trauma 2014*   *Cap Nato BP Meeting May 2018*

From « what should be » to « what is in practice »

13 mars 2018 — JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE — Texte 17 sur 124

Décrets, arrêtés, circulaires

TEXTES GÉNÉRAUX

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

Décision du 8 février 2018 fixant la liste et les caractéristiques des produits sanguins labiles

HAS HAUTE AUTORITÉ DE SANTÉ

ansm Agence nationale de sécurité du médicament et des produits de santé

RECOMMANDATION DE BONNE PRATIQUE

Transfusion de globules rouges homologues : produits, indications alternatives

Méthode Recommandations pour la pratique clinique

Gap analysis

➢ WB is **authorized** (Official Journal 2018)

➢ WB has no **indications** (Guidelines 2014)

➢ Bring evidences to this Agency in order to implement WB in the guidelines on the management of traumatic massive hemorrhage

What could be the benefits for the patients?

1. **Plasma would be transfused earlier** in hospitals that do not have dried or prethawed plasma

2. **Platelets also would be transfused earlier** as they are often provided after the 3rd pRBCs, and regarding these platelets, maybe their storage at 4°C will be more convenient to treat coagulopathy

3. **Less anticoagulant and storage solution** will be transfused
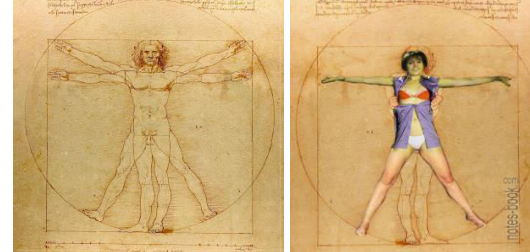
4. **Simplify the work** for the nurses

STORHM Study

- Prospective – **randomized**

- Multisite – **6 trauma centers**
  - MMC Percy and Sainte Anne
  - PPH Kremlin-Bicêtre and Pitié-Salpétrière
  - UH Brest and Grenoble

- Promoted by the **2 French transfusion operators**
  - French Military Blood Institute (CTSA)
  - French Blood Establishment (EFS)

STORHM Study: population studied

Inclusion criteria: A <u>and</u> B

A - All **trauma** patients justifying the activation of the highest prehospital level of care

B – One of the followings:
- The activation of a **massive transfusion protocol**
- And/or the transfusion of **at least one unit of pRBC in the emergency room**
- And/or a **predicted need of at least 4 pRBC in the first 6 hours** as assessed by ABC score

➔ The combination of these 3 criteria represent 10-15% of the **A** population

Exclusion criteria

- Hemorrhage from non traumatic cause
- Patient taking an anticoagulant drug
- Pregnancy
- Age < 18 or weight < 50 kg if unknown age
- Prisoners
- Patient refusing transfusion
- Transfer from another center

STORHM Study: blood products

- **O group** Whole blood
- Hemolysins **low titer** (< 1/64 in France)
- RH-1 only for women under 50 y
- In **CPD –** from **male donors**
- **Leukoreduced** with a sparing platelets filter (Imuflex SP, Terumo)
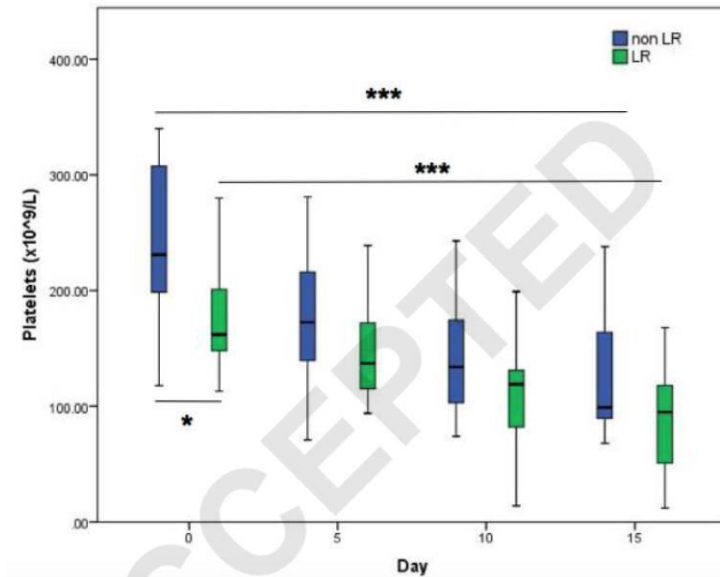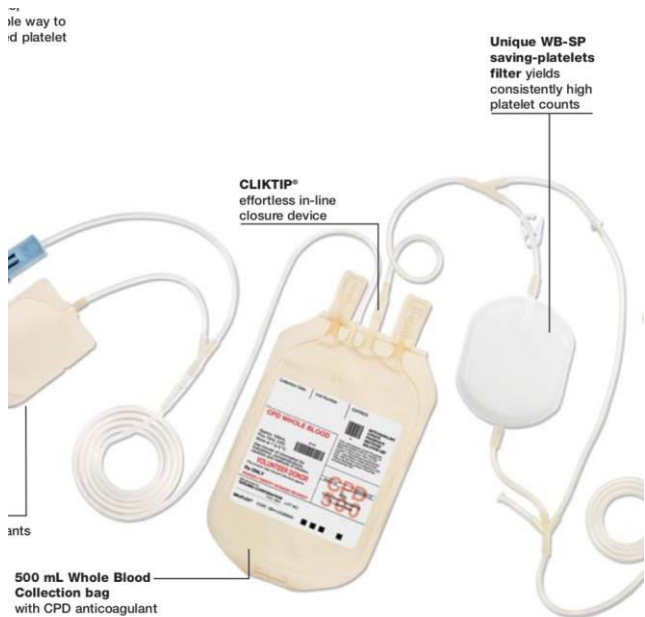- Stored up to **21 days** : 7 or 14 days in STORHM

Recycled in RBCs after 7 or 14 days into packed red blood cells

Wastage of FWB is expected : **50%**

- ➢ O group RBCs are too valuable to be wasted
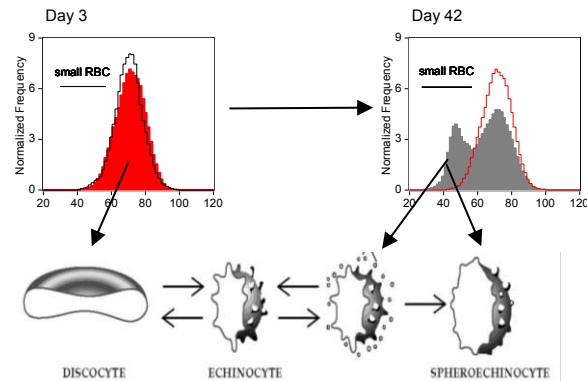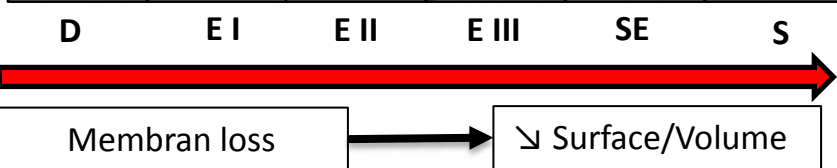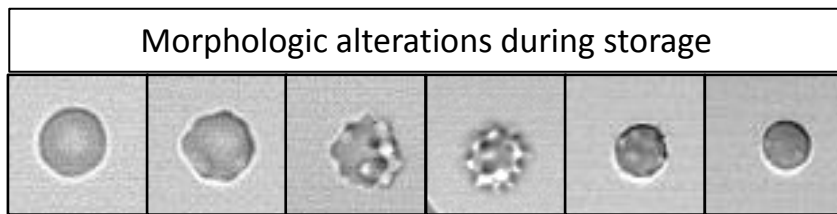- ➢ Compels us to investigate the in vitro quality of blood products

LR units. The clinical relevance of these findings is difficult to know with precision, though it is

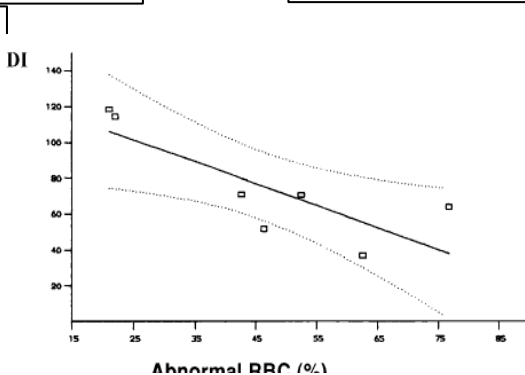clear that LR did not improve PLT function. While there are reports indicating that changes in

Remy et al. J Trauma 2018 and Zielinski et al. J Thrombo Cir 2018

STORHM Study: blood products Quality Control of recycled RBCs

Morphologic alterations during storage

D   E I   E II   E III   SE   S
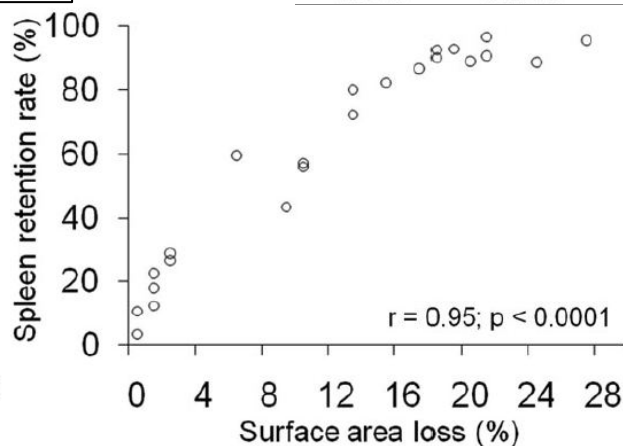
Membran loss → ↘ Surface/Volume

Day 3   Day 42

Correlation between RBCs morphology and post-transfusion clearance

Haradin et al, 1969

Correlation between morphology and RBCs deformability

Berezina et al, 2012

Human spleen perfusion

r = 0.95; p < 0.0001

Safeukui et al. Blood 2008   *Roussel et al. Transfusion 2017*

The main issue was the incompatible plasma transfuse to non-O patients

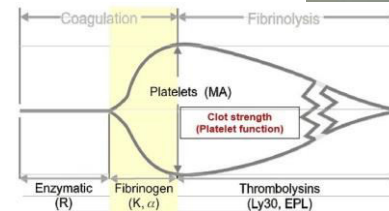**We decide to transfuse up to 6 units of WB based on:**

1. **Our massive transfusion protocols** consist of 6 pRBCs-6 plasma and 1 platelet, the latter being transfused after 3 RBCs and 3 plasma

2. If we believe that the advantage of WB transfusion relies partly on bringing platelet earlier then **3 units may be not enough**

3. **Data on safety are available** from:
   1. incompatible platelet in plasma transfusions
   2. incompatible plasma in emergency situations
   3. recent studies on the use of FWB

- On average, in France those patients require a **median of 7 units of RBCs** [IQR: 5-10] during the first 6 hours

- Resume the component therapy with O-group RBCs until compatibility test <0

Seheult et al Transfusion 2018 - Stevens et al J Trauma 2017 - Balvers et al. Transfusion 2016 – Dunbar et al. Transfusion 2017

STORHM Study: primary endpoint

- **The best primary endpoint: mortality at 6 hours**
  - You will need more than **400 patients per arm**
  - Regarding the incidence of trauma with hemorrhage in France, this endpoint was unfortunately **unrealistic**.
- **Easy to assess: biological endpoints**
  - **Lactates** clearance. However, based on our data this test was discarded.
  - **Maximum Amplitude measured on a TEG6S** because it takes into account
    1. the early supply of **platelets**
    2. the **hemostatic** properties of a whole blood-based resuscitation protocol
    3. Correlated to mortality and blood products use
    4. **easy** to perform

- Sample sizing calculation = **82 patients per arm**
  - Non inferiority trial
  - Less than 5 mm allowed
  - *n = f(α, β) × 2 × σ2 / d2 where alpha is the first species risk (fixed at 5%), beta the power (fixed à 80%), sigma the standard deviation of the continuous variable and d2 the maximal accepted difference*

STORHM Study: secondary endpoints

1. Safety by monitoring (48h) the levels of:

- Haptoglobin,
- LDH,
- Bilirubin
- Coombs tests

2. Easiness of use

- A questionnaire could be helpful but is always hard to implement correctly.
- We decided to evaluate the time interval needed to transfuse the first unit of WB compared to the first plasma unit and the first platelet unit as a surrogate marker

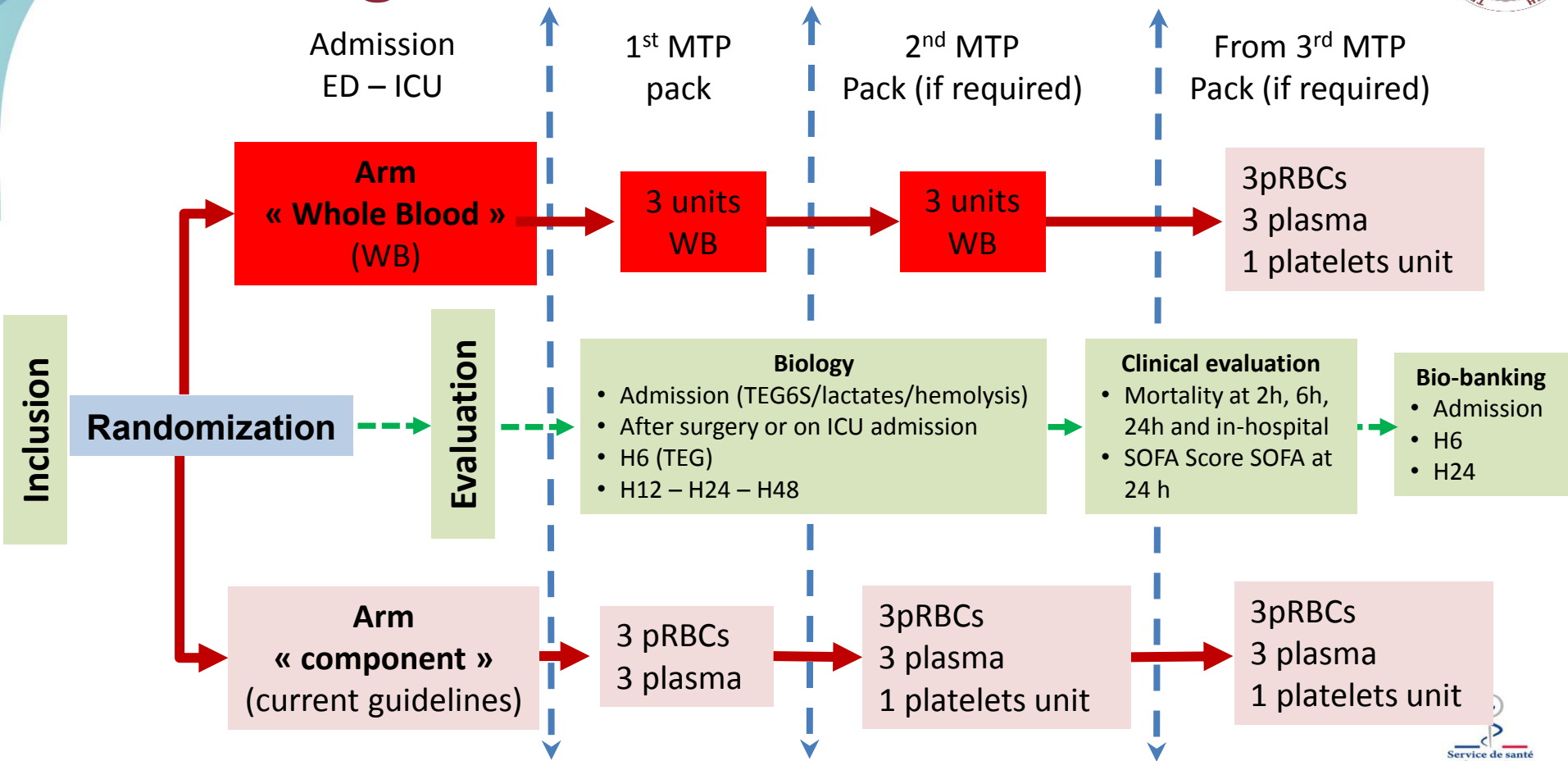**3.** All-cause **mortality** 2 hours after admission and 30 day mortality

4. Proportion of patients dead at 24 hours or presenting a **multi-organ failure** with a SOFA score > 12

5. Proportion of patients successfully resuscitated with a **lactate clearance >20%**

6. The **amount of red blood cells** transfused in the first 24 hours

7. Direct **cost** of transfusion

Service de santé
des armées

Design

Acknowledgments

- **French Military Blood Institute**
  - E. Garrabé
  - C. Civadier
  - O Javaudin
  - T. Pouget
  - E. Dedôme
- **Etablissement Français du Sang**
  - S. Gros
  - P. Tiberghien
  - B. Bonneaudeau
  - S. Begué

- **Military Medical Centers**
  - S. Ausset (Percy)
  - E. Meaudre (Toulon)
  - S. Pons (Toulon)
- **Imagine – INSERM U1163**
  - P. Amireault
- **INTS – UMR-S1134**
  - C. Roussel
  - Pierre Buffet
- **Armed Forces Medical Research Institute**
  - A. Sailliol
  - N. Prat

- **Paris Public Hospitals**
  - J. Duranteau (KB)
  - M. Raux (Pitié)
- **University Hospitals**
  - Y. Ozier (Brest)
  - P. Bouzat (Grenoble)

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