

TRANSFUSION MANAGEMENT FOR MASSIVE HAEMORRHAGE

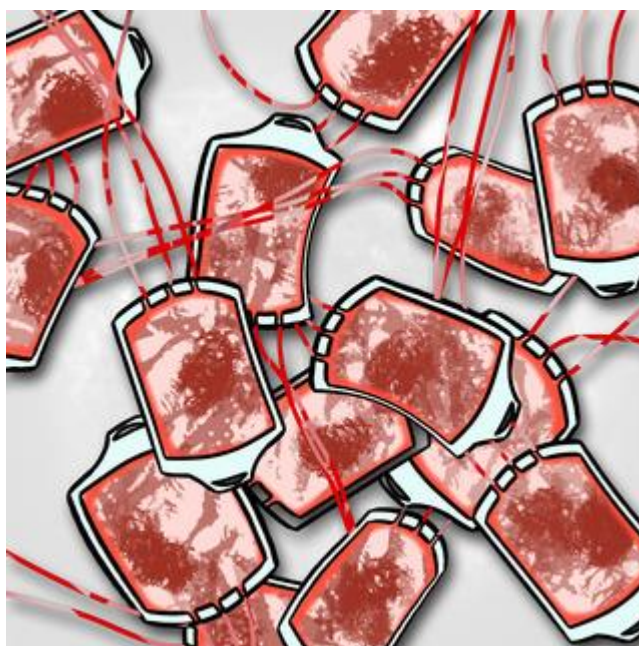
PROTOCOL

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1. INTRODUCTION

Uncontrolled and massive haemorrhage is one of the major challenges in the field and a leading cause of early hospital deaths. This excess mortality might be preventable by putting more efforts on an effective therapy and timing of interventions. While majority of trauma patients do not require a massive transfusion (MT), patients who do require a MT have a significantly increased morbidity and mortality.

Massive haemorrhage has been variously defined as ^{[1], [2], [3]} :

- Loss of more than one blood volume within 24 hours (around 70 mL/kg, >5 litres in a 70 kg adult).
- 50% of total blood volume lost in less than 3 hours.
- Bleeding which leads to a SBP of less than 90 mmHg or a heart rate of more than 110 bpm.

A more pragmatic and clinically meaningful definition of massive haemorrhage/massive transfusion is:

Transfusion of 3 units of whole blood (WB) or 4 units of packed red blood cells (PRBC) in the first hour and further blood components are expected to be needed.

Or a rate of loss of over 150 mL/min (i.e. flowing as fast as pouring a cup of water on the floor).

Early recognition and intervention are essential for survival of patients with massive haemorrhage. While this document focuses on blood product management and adjuvants, as well as inter-department coordination, other measures are detailed in [Damage Control Resuscitation \(DCR\) for Trauma Protocol](#).

The assessment that a haemorrhage is life-threatening is mainly established clinically and should be driven by an assessment of the patient's vital signs, haemodynamics, physical exam, mechanism of injury, and if available, laboratory assays of shock and haemostasisⁱ.

The immediate priorities are to:

- Control bleeding (compression, tourniquet, surgery) C-ABC
- Early blood transfusion
- Prevent the lethal triad: hypothermia, acidosis, coagulopathy
- Early tranexamic acid when indicated

Successful management of massive haemorrhage requires a protocol-driven team approach with involvement of medical and nursing staff, laboratory staff (including blood bank) and support staff (e.g., stretcher bearers, health promotion team) to ensure clear and efficient lines of communication between clinicians and the blood bank, and timely delivery of blood products. ^[34]

2. BLOOD PRODUCTS & ADJUVANTS

2.1 WHOLE BLOOD

Whole blood (WB) delivers all the components of blood in the correct ratio and would be the ideal resuscitation fluid for massively bleeding patients as it restores circulatory volume, contains active clotting factors, and is a source of platelets.

- **STORED WHOLE BLOOD (SWB)**

SWB is the most commonly available form of WB in MSF contexts. The shelf life of SWB is determined by the capacity of the anticoagulant solution to sustain red blood cell (RBC) integrityⁱⁱ. SWB simplifies the logistics of transfusion and may facilitate more rapid resuscitation of bleeding patients and may enhance a facility's capacity to manage mass casualty incidents ^{[19], [21], [7]}. SWB should however be divided into:

- **Stored whole blood that has been recently collected (up to 7 days after collection)** generally retains full haemostatic capacity, most notably platelet function ^[5].
- **Stored whole blood collected between 7 to 35 days:** After the first week of storage, the haemostatic capacity of WB may vary and supplementation with fresher whole blood units or blood components, especially platelets (PLTs), may be necessary to promote haemostasis ^{[Error! Reference source not found.], [8], [9]}.

ⁱ Peripheral blood haematocrit and Hb concentration can be misleading early after major acute blood loss and the initial diagnosis of massive haemorrhage requiring transfusion should be based on clinical criteria and observations.

ⁱⁱ SWB can be stored for 35 days at 2–6°C in CPDA-1 (citrate phosphate dextrose adenine).

- **FRESH WHOLE BLOOD (FWB)**

FWB refers to WB collected less than 4 hours prior to use and has not been refrigerated. It can be refrigerated within 4 hours of collection, after which point it becomes SWB. FWB is considered to have full haemostatic function. The availability of FWB may be limited due the constrained pool of donors who must be tested for transfusion transmitted diseases and blood-type grouping. It can be collected on an emergency basis from pre-screened donors, i.e. “walking blood bank” [3], [10].

- **BLOOD BANK MANAGEMENT**

A dedicated blood bank process for massive transfusion should be implemented in projects where such practice is warranted (e.g., trauma, mass casualty, and OB-GYN). Physical separation of recently collected whole blood (up to 7 days after collection) and “usual” whole blood (collected between 7 to 35 days) should be carried out using separate storage boxes for each category of WB. Close collaboration between the blood bank personnel and medical/surgical staff is essential [10].

2.2 BLOOD COMPONENT THERAPY

Blood component therapy is an acceptable alternative for treating life-threatening haemorrhage when WB (FWB or SWB < 7 days) is not available. This strategy entails the transfusion of fractionated blood products in ratios that correspond to that of WB (1:1:1). The potential for reduced efficacy and safety, as well as the logistical imperatives of blood component therapy, should be taken into consideration when choosing a transfusion strategy for resuscitation in massive haemorrhage. It is worth noting that the volumes of anticoagulant-preservative and additive solutions in the units of blood components are significantly higher than the volume of CPDA-1 added to a single unit of WB ⁱⁱⁱ. This extra volume of citrate and anticoagulant, which is also non-oxygen-carrying, can result in a deleterious expansion of the patient’s total extracellular fluid compartment. Components do not need to be released from the blood bank at the same time as the preparation of plasma and platelets may take longer than PRBCs, which are usually ready first.

- **RED CELLS**

Packed red blood cells (PRBCs) are not available in all MSF contexts and are generally obtained by sedimentation of WB bags which serves to separate plasma from concentrated red cells. PRBCs in massive haemorrhage resuscitation need to be transfused in association with other blood components in ratios that correspond to that of whole blood (i.e. ratio of 1:1:1 for units of PRBC: plasma: platelets) to promote haemostasis and to maintain coagulation and circulatory volume.

- **PLASMA**

Fresh frozen plasma (FFP) provides coagulation factors with the secondary benefit of volume resuscitation. Standard FFP contains 2-5 mg/mL of fibrinogen. FFP should be thawed between 30 and 37°C in a water bath under continuous agitation. To make up for the delay imposed by slow thawing of FFP (up to 30 minutes or more), pre-thawed FFP can be stored refrigerated for up to 5 days. However, this can lead to significant waste of products.

Group AB plasma is classically considered to be universally compatible plasma. Group A plasma can, however, be used safely in emergency settings in the absence of compatible plasma, or AB plasma, as evidence suggests that only low levels of Anti-B are produced in most group A donors. The order of preference for FFP transfusion is: ABO compatible, Group AB, Group A [11]. As FFP does not contain red blood cells, there is no need for cross matching.

FFP is usually transfused in doses of 15 mL/kg (at least four units in the average adult) to maintain the INR (International Normalized Ratio) less than 1.5. In a MTP situation, FFP needs to be associated to other blood components in ratios similar to whole blood in a fixed ratio (i.e. 1:1:1 for units of PRBC: plasma: platelets) ^{iv}.

- **PLATELETS**

A dilutional effect on the platelet concentration can be seen with massive transfusion. In an adult, platelet counts below $50 \times 10^9/L$ can be expected when approximately two blood volumes have been replaced by crystalloid fluids or red cell components. Thus, an early platelet transfusion trigger and balanced transfusion strategy in patients

ⁱⁱⁱ A 450 mL bag of WB is diluted with 63 mL of citrate-phosphate-dextrose-adenine (CPDA-1) solution required to preserve RBC viability for 35 days of refrigerated storage.

^{iv} Freeze-Dried Plasma (FDP) can be an alternative for early plasma transfusion in environments where FFP is not immediately available. FDP is produced by freeze-drying or spray-drying liquid or thawed plasma and remains shelf-stable at room temperature for prolonged periods.

with ongoing bleeding is recommended with a target platelet level of $75 \times 10^9/L$. A higher target level of $100 \times 10^9/L$ is recommended for patients with a central nervous system (CNS) injury. In a MTP situation, platelet units need to be associated to other blood components in ratios similar to whole blood in a fixed ratio (i.e. 1:1:1 units of PRBC: plasma:platelets). Note that 1 unit of apheresis platelets is equivalent to 6 units of non-apheresis (i.e. platelet concentrates or random donor or whole-blood derived platelets)^v. They can be stored for up to 5 days at 22°C.

2.3 GROUPING/CROSSMATCHING

ABO group-specific blood should be given at the earliest possible opportunity, ideally before any transfusion. Blood group determination can be performed very quickly in the field; therefore, it should not be necessary to give large volumes of group O blood.

- In life-threatening emergencies and mass casualty incidents, where blood is required immediately in exceptional clinical circumstances and the blood group is unknown, use group O Rh-D positive uncrossmatched blood, except in women of child-bearing age as described below.
- Females under 50 years of age whose blood group is unknown should ideally be given group O Rh-D negative blood if available in order to avoid Anti Rh allo-immunisation and the risk of haemolytic disease of the newborn in subsequent pregnancy. However, it remains possible to use O positive in life threatening situations^{[12], [13]}.
- In most MSF contexts, as the prevalence of Rh-D negative is low (between 2 and 8 %), the risk of transfusing with non-compatible Rh is also low.
- Then transfuse ABO Rh- D specific blood as soon as the blood group is available.

2.4 CELL SALVAGE / AUTO-TRANSFUSION

Autotransfusion of shed blood can be a safe technique in which blood from a bleeding patient is collected and reinfused into the same patient. Simplified techniques can be an alternative to allogeneic transfusion in resource-limited settings, and is described for patients with haemothorax, ruptured ectopic pregnancy, and injuries to the liver or spleen without intestinal perforation^{[13], [15]}.

2.5 ADJUVANTS

• *TRANEXAMIC ACID (TXA)*

Empiric use of Tranexamic acid reduces mortality if given within a **3-hour** window in the following situations of massive haemorrhage:

- Trauma-associated haemorrhage^{vi}.
- Postpartum haemorrhage (PPH).

It may also be considered in the following indications:

- Gastrointestinal haemorrhage.
- Surgical bleeding in major orthopaedic, thoracic, abdominal, urological, and maxillofacial surgery.

Initial dose, in all cases, 1 g slow IV should be given over 10 minutes ideally (15 mg/kg in children). In the case of trauma, the initial bolus should be followed by another 1 g dose infused over 8 hours. In PPH, if bleeding continues 30 minutes after initial TXA administration, a second dose of 1 g should be given^{[16], [17], [18]}.

• *CALCIUM*

Calcium is a key adjuvant needed in the clotting cascade. Citrate in blood products chelates calcium, leading to hypocalcaemia which causes coagulopathy. When blood is infused rapidly and because the liver function might be impaired by the haemorrhagic shock state, citrate may temporarily accumulate and promote hypocalcaemia. Moderate hypercalcaemia is well tolerated. Therefore, the therapeutic target is a high-normal level of calcium (in a massively haemorrhaging patient, it's probably better to err on the hypercalcaemic side).

Calcium gluconate should be given systematically after the two first units of blood in adults (after 20 mL/kg of WB or 15 mL/kg of PRBC in children).

^v Non-apheresis platelets (or platelet concentrates or pooled random donor platelets) are made by combining 6 to 10 platelet units with the same ABO type from multiple donors into a single bag for transfusion. Apheresis platelets are collected from a single donor and are equivalent to ~4-6 pooled units. Platelet components are suspended in plasma that contains the anti-A and anti-B isoagglutinins, they should therefore be ABO compatible with the recipient's PRBCs.

^{vi} TXA given > 3 hours post-injury increases the risk of mortality.

Initial dose 1g by slow IV (In children < 10 kg - 0.5 mL/kg; and from 11 to 45 kg - 0.3 mL/kg). Subsequent doses should ideally be guided by lab levels with a target of ionised Calcium of > 1 mmol/L. In the absence of lab assays, calcium gluconate can be pre-emptively repeated at the same dose every 2 units of transfused blood products ^{vii}.

3. MASSIVE TRANSFUSION PROTOCOL

Massive transfusion of blood products is a key part of the damage control resuscitation paradigm conceived to manage severely ill patients.

The Massive Transfusion Protocol (MTP) is a cognitive aid to focus the clinical team on the timing for initiation of blood product transfusion and the optimal ratio of product administration, with the aim of maintaining organ perfusion and oxygen carrying capacity, reducing the incidence of multi-organ failure, while at the same time reducing blood product use and wastage. Ultimately, the application of such MTPs has been shown to reduce early mortality from massive haemorrhage ^{[19], [20]}.

MTP is a system or process that includes:

- standardised triggers for initiating MTP.
- ratio-based blood product administration (haemostatic resuscitation), avoiding use of unnecessary and potentially harmful crystalloids or colloids ^{viii}.
- blood bank processes for communication, MTP product availability, including immediate availability of group O blood products, and MTP product delivery.
- transfusion targets.
- use of adjuvants for massive transfusion patients.
- prevention of acidosis, hypothermia, and hypocalcaemia.
- termination of the MTP.

In an emergency, it is essential to ensure that correct transfusion identification procedures for patients, samples and blood components be performed, and an accurate record kept of all blood components transfused.

3.1 ACTIVATION

The assessment that a haemorrhage is life-threatening is mainly established clinically and should be driven by an assessment of the patient's vital signs, haemodynamics, physical exam, mechanism of injury and laboratory results for shock and altered haemostasis if available.

A key factor in the effectiveness of the MTP is the timely and appropriate initiation of the protocol. The earlier the appropriate transfusion of blood products is initiated, the better the chances of survival.

A coordinator should be designated for communicating with the laboratory blood bank and other support services to prevent time-wasting and duplicate requests. Laboratory blood bank and other relevant departments should put in place standard operating procedures to ensure that clinical and non-clinical staff ^{ix} are contacted appropriately and are aware of the timeframe within which blood is needed at the bedside (i.e., immediately, within 20 min, within an hour).

MTP activation is a medical decision and should be performed by the medical team caring for the patient (often the most senior doctor) based on clinical and physiological factors ^{[21], [22], [2223]}.

Currently, there is no international consensus on which activation criteria or scoring system should be used to anticipate the need for a massive transfusion. Various scoring systems have been proposed with varying degrees of complexity, sensitivity and specificity. However, the criteria proposed below have been shown to be superior to clinical judgement alone ^{[2219], [22]}.

Laboratory values are only supportive data for decision making in the MTP and are not required to activate the protocol. Waiting for laboratory results can lead to unnecessary delays. Although a haemoglobin level under 11g/dL has been shown to be predictive of a need for MT in the context of massive bleeding, baseline and repeated measurements cannot be relied upon solely to guide the decision to trigger an MTP and should not delay such decision.

^{vii} Calcium gluconate should be given in a separate IV line from blood components.

^{viii} Synthetic colloids, such as Gelofusine, should not be used nor are they a substitute for blood products.

^{ix} Porters or stretcher bearers play an important role in the logistical challenge of timely delivery of blood products to the bedside.

MTP should be activated if:

- **Massive haemorrhage** clinically obvious (e.g., post-partum or intra-operative bleeding, pulsatile bleeding, positive FAST...)
- OR
- **Severe mechanism of injury** (e.g., proximal amputation, penetrating mechanism of injury, unstable pelvic fracture...)

PLUS, haemodynamic instability reflected by one of the following:

- systolic blood pressure less than 90 mmHg (or age-specific value)
- pulse rate over 120 beats per minute (or age-specific value)
- shock index (HR/SBP) > 0.7
- temperature < 36°C
- abnormal mental status

OR coagulopathy reflected by one of the following:

- uncontrolled bleeding
- bleeding at injection sites
- INR < 1.5

3.2 STEP 1

- Draw blood samples and send for labs:
 - Hb level, blood group determination and crossmatch.
 - platelet count, INR, ionised calcium, and potassium (if available).
- Order, warm and transfuse, in order of preference:
 - **2 WB** - FWB or SWB (less than 7 days).
 - **Or 2 PRBC: 2 FFP: 2 PLT.**
- Administer TXA (see concurrent therapy).

If the patient is still haemodynamically unstable, or if bleeding persists, continue to “STEP 2”

3.3 STEP 2

- Order, warm and transfuse, in order of preference:
 - **4 WB** - FWB or SWB (less than 7 days).
 - **Or 4 PRBC: 4 FFP: 4 PLT.**
- Give 1 g calcium gluconate (see concurrent therapy).
- Laboratory blood bank should actively manage blood stock, identify, and test potential compatible blood donors, and request urgent resupply if appropriate. Pre-identified donors in the community or “walking blood bank” can be an effective strategy to ensure an adequate blood supply.
- Monitor CBC, renal function, and if available, acid-base status, electrolytes (calcium and potassium levels should be aggressively managed).

If the patient is still haemodynamically unstable, or if bleeding persists, continue to “FOLLOWING STEPS”:

3.4 FOLLOWING STEPS

- Repeat all of STEP 2 with ABOD compatible units.
- If the supply of ABOD compatible units becomes a challenge, refer to [Table 1.1 ABO Compatibility Rules in the 2019 MSF Blood Transfusion Guideline](#).
- Continual reassessment of the patient’s condition is needed during and between transfusions. As the patient stabilises, component and active bleeding becomes more controllable, ratios should be replaced by ‘goal-directed’ therapy guided by laboratory evaluation:
 - Hb > 7 g/dL.
 - Platelets > 75 x 10⁹/L (100x 10⁹/L if CNS injury).
 - If available: INR < 1.5; Ionised Calcium > 1mmol/L; Fibrinogen > 1.5 g/L.

3.5 CONCURRENT THERAPY

Concurrent therapy should occur simultaneously with STEP 1 & 2, and following steps. Patients are at high risk of developing hypocalcaemia, metabolic acidosis, hypoglycaemia, hypothermia and hyperkalaemia during MTPs. Therefore, frequent monitoring and correction of acid/base status, electrolytes, and core temperature is essential during the resuscitation of these patients.

Other measures are detailed in [Damage Control Resuscitation \(DCR\) for Trauma Protocol](#) and include the following:

- **Haemorrhage control:** Stop/limit the source of bleeding via compression, dressing, tourniquet, extravascular balloon tamponade, pelvic binder, intra-uterine Bakri balloon tamponade, damage control surgery...
- **TXA:** Administer within 3 hours of onset of bleeding - give 1 g by slow IV bolus over 10 min (children 15 mg/kg).
- **Calcium gluconate:** Give 1-2 g by slow IV over 15 min, after 2 first units of blood (children 0.3 mL/kg). Following doses should ideally be guided by lab levels with a target of ionised Calcium of > 1 mmol/L. Calcium can be empirically repeated in the absence of labs with 1 g slow IV every 2 units of blood.
- **Active warming:** Target core temperature > 36°C.
 - Stop air conditioning.
 - Use emergency/warming blanket.
 - Use forced air warming blanket.
 - Use blood/fluid warmer device.
- **Other measures:**
 - Avoid excess crystalloid infusion.
 - Prevent acidosis (e.g., higher minute ventilation for intubated patients. Target pH > 7.35 if available).
 - Prevent or treat hypoxia (target SpO₂ > 95%).
 - Monitor Hb, platelets, urea, creatinine and if available, coagulation and electrolytes. Calcium and potassium levels should be aggressively managed.
 - Maintain a permissive hypotension (SBP of 80 to 100 mmHg), until hemorrhage control is obtained (in the absence of associated traumatic brain injury or spinal cord injury).

3.6 TERMINATION

- To avoid over-transfusion, it is essential to carefully monitor the patient's vital signs and laboratory assays. This monitoring includes recognizing a developing or resolving coagulopathy using clinical observation, standard coagulation tests.
- Stop massive transfusion protocol when all the following criteria have been reached:
 - Absence of haemorrhage or disseminated intravascular coagulation (DIC).
 - Haemodynamic stability.
 - Adequate results for Hb (>7 g/dL), platelets (>75 x 10⁹/L).
 - and if available coagulation tests (INR < 1.5 the reference value, Fibrinogen > 1.5 g/L).
- The MTP should not be continued if the patient's condition deteriorates to the point that survival is unlikely and further transfusions become futile ^x.

3.7 PAEDIATRIC CONSIDERATIONS

The circulating blood volume in children may vary between 70 to 90 mL/kg (see table).

Age range	Preterm	Neonate	4 months – 2 years	> 2 years
Circulating blood volume	90 mL/kg	80-90 mL/kg	70-80 mL/kg	70-75 mL/kg

For children under a weight of 20 kg, transfuse WB, PRBCs, FFP, or platelets with volumes as follows:

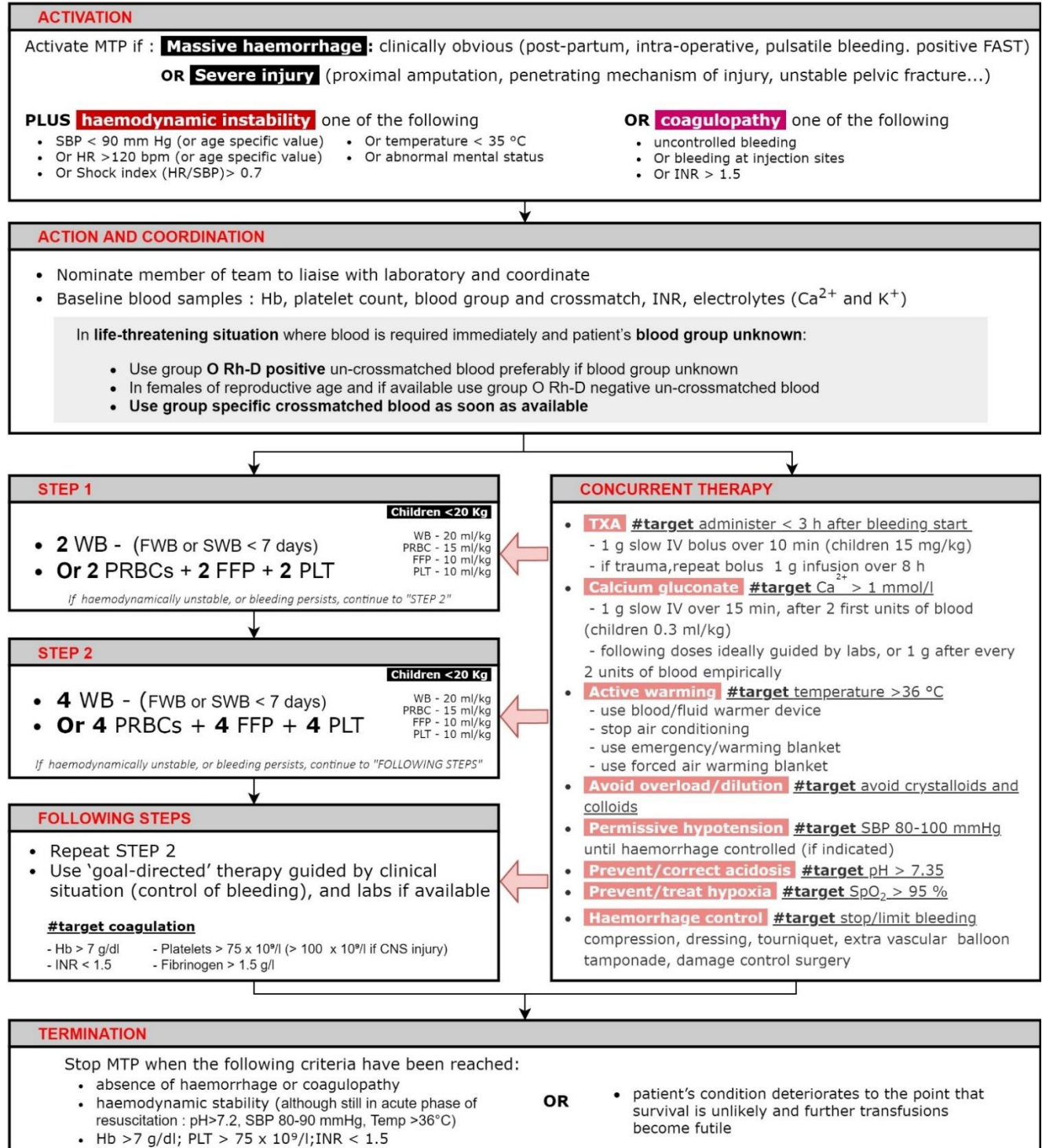
- Transfuse
 - 20 mL/kg WB.
 - Or 15 mL/kg PRBC: 10 mL/kg FFP: 10 mL/kg PLT.
- If necessary, repeat the transfusion of the blood components as above according to clinical criteria and/or laboratory results (same parameters as for adults).

^x There is no clear threshold beyond which blood usage is futile. There is, however, a need to ensure that blood stocks are not exhausted.



Transfusion Management of Massive Haemorrhage

EMACC - Emergency Medicine Anaesthesia Critical Care - Working Group
Laboratory - Working Group



ABBREVIATIONS:

BPM: beats per minute; Ca²⁺: ionized Calcium; CNS: central nervous system; FAST: focused assessment with sonography in trauma; FFP: fresh frozen plasma; FWB: fresh whole blood; Hb: haemoglobin; HR: heart rate; INR: international normalized ratio; MTP: massive transfusion protocol; PLT Platelets; PRBC: packed red blood cells; PT: prothrombin time; Rh: rhesus; SBP: systolic blood pressure; SWB: stored whole blood; TXA: tranexamic acid; WB: whole blood.

Access poster version here: [MSF Transfusion Management of Massive Haemorrhage Protocol 2021](#)

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